Bone and Joint Disorders

(BONE AND JOINT DISORDERS)

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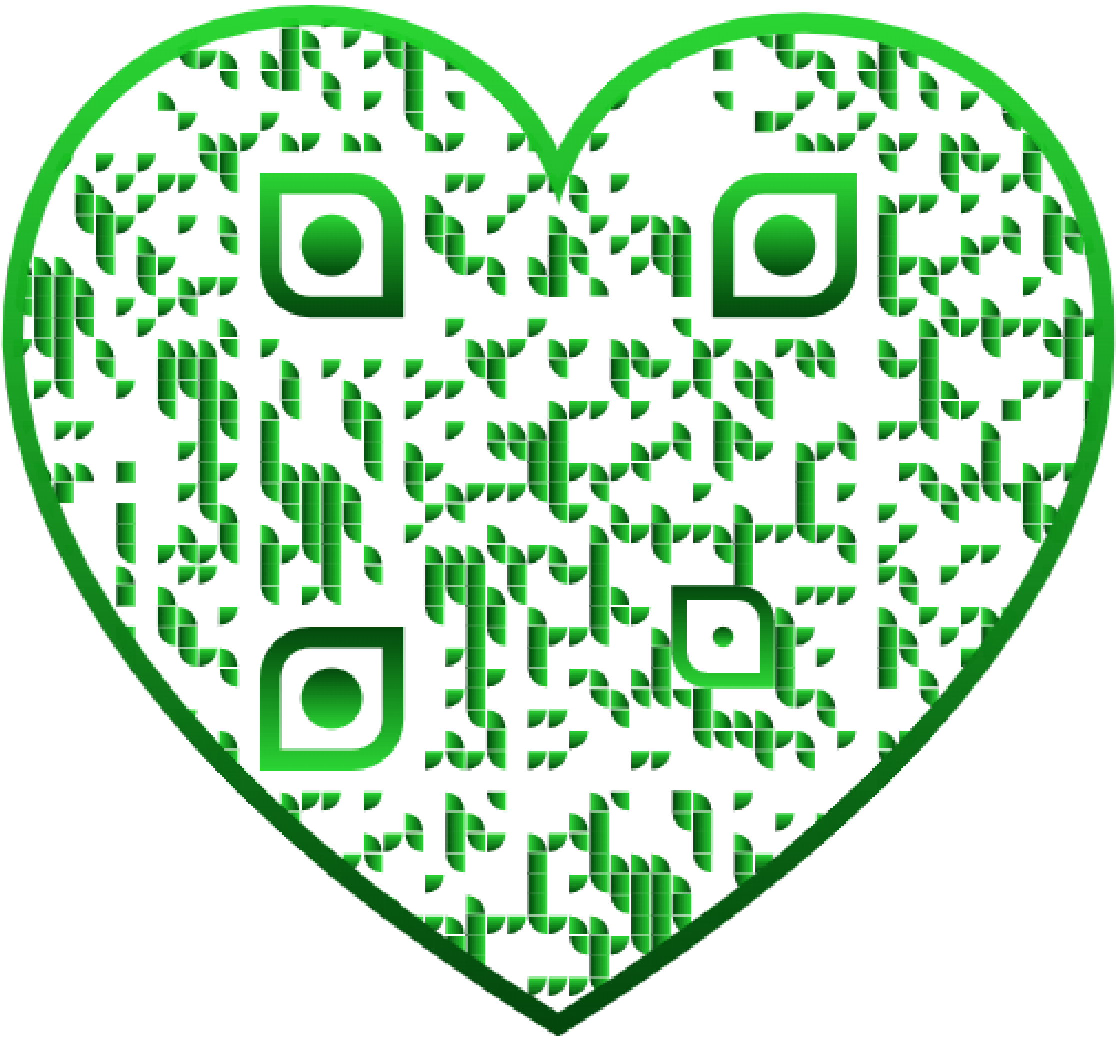
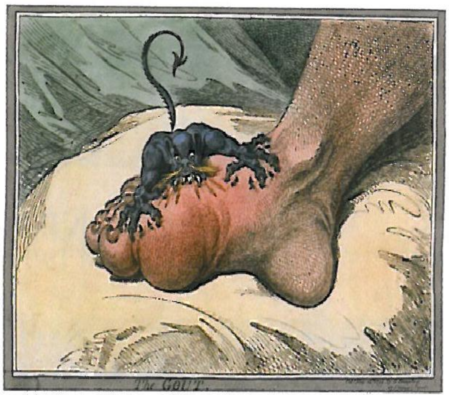


Gout and Hyperuricemia

➤ Overview:-

- **Gout** is *characterized by* ***sudden, severe*** **attacks** of **pain**, **redness** and **tenderness** in **joints** (often the joint at the base of the **big toe**).
- The ***term*** **"Gout"** was used, *around* **1200 AD** (Anno Domini). It is derived from the ***Latin word*** **"Gutta"** meaning **"a drop"** = *"dropping of a morbid material from the blood in and around the joints"*.
- The ***first documentation*** of the disease is from **Egypt** in **2,600 BC** (Before Christ) in a description of **arthritis of the big toe**.
- ***Historically***, **gout** has been ***referred to*** as the "**disease of kings**", since it was often *associated with* **affluent societies**.



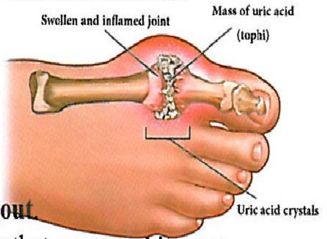
The Gout (James Gillray, 1799) depicts the pain of the artist's podagra as a demon or dragon.

➤ Definitions:-

- **Hyperuricemia** [hyper-yur-i-see-me-ya]; is an ***abnormally*** **high level** of **Uric Acid** (**UA**) in the blood; ***Reference range***; **Male**; 3.5–8.0 mg/dL. **Female**; 2.5–6.5 mg/dL.
  - **American college of rheumatology** (**ACR**) ***definition*** of **hyperuricemia**; **Serum Urate** (**Uric Acid**) **level** ***greater than*** either **6.8** or **7.0 mg/dl**.
  - **Hyperuricemia** is ***not a disease*** and may ***not cause*** problems, but if it ***continues*** for a **long time** ***may cause*** **gout**, so *most experts* ***recommend*** that **Uric Acid** ***levels*** stay below 6.0 mg/dL in order to ***prevent*** **gout**.
- **Gout**; is a *crystal-deposition disease* that *results from* **chronic elevation** of **Uric Acid** ***levels*** **"hyperuricemia"** (serum urate level more than 6.8 mg/dL or 7 mg/dL), *resulting in* ***tissue deposition*** of **Mono-Sodium Urate Monohydrate** ***crystals*** in the ***extracellular fluid*** of **joints** and **other sites**.
  - *N.B.*; **Pseudogout** or **Calcium Pyro-Phosphate Disease**; is caused by **Calcium Pyro-Phosphate** ***crystals***.

➤ Gout Prevalence:-

- **Gout** is the ***common*** **rheumatic disease** or **inflammatory arthritis** in adults.
- **Gout** is ***common*** in **most countries** in North America and Western Europe, with prevalence in the range **1-4%**.
- **US adults** in **2007–2008** was **3.9%** (**8.3 million**).
- ***More than*** **2 million** people in the US take **medication** to ***decrease*** **serum Uric Acid** ***levels***.
- *Approximately* **20%** in ***patients*** with a **family history** of **gout**.
- The ***incidence*** of **gout** among **black men** was *almost* ***twice*** that among **white men**.
- **Gout** ***affects*** **men** *about* **7- 9 times** ***more often*** than **women**.
- The ***incidence*** of **gout** ***increases with*** **age**, peaking at **30 to 50 years** of **age**.



➤ Gouty Arthritis and Hyperuricemia Relationship:-

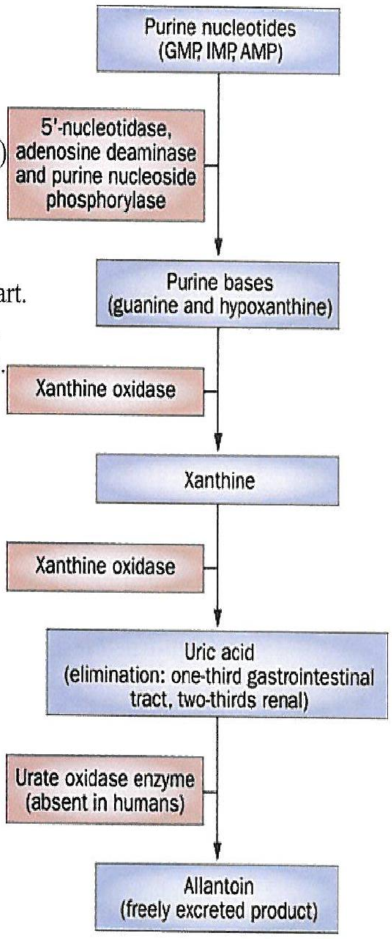
- ***Hyperuricemia*** is caused by an ***imbalance*** in the **production** and **excretion** of **Uric Acid** (i.e., overproduction, under-excretion or both).
- ***Elevated*** **serum Uric Acid level** may ***indicate*** an ***increased risk*** of **gout**.
- ***Many*** **patients** with **hyperuricemia** ***do not develop*** **gout** (Hyperuricemia is not the same as gout).
- ***Some patients*** with ***repeated gout attacks*** have ***normal*** **blood Uric Acid levels**.
- The ***treatment of*** **gouty attack** is ***different than*** the ***treatment of*** **hyperuricemia**.
- The ***relationship between*** **hyperuricemia** and **gout** is ***unclear***.
- ***Asymptomatic*** **hyperuricemia** ***does not need*** to be **treated**, **lifestyle measures** are ***needed***.
- **Gout** is ***diagnosed clinically*** by ***symptoms rather than*** **laboratory tests** of **Uric Acid**.

➢ Causes of Hyperuricemia:-

- **In humans**, the *production* of **Uric Acid** is the ***final step*** in the ***degradation*** of **purines**.
- ***Causes of hyperuricemia***;
  1) ***Increased*** **production** of **Uric Acid**.
  2) ***Decreased*** **excretion** of **Uric Acid**.
  3) ***Mixed*** (increased production and decreased excretion).

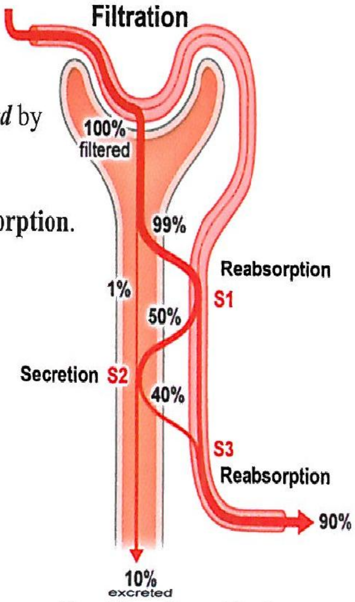
- ***Increase*** **production of uric acid**; (about 10% of cases)
  1) **Dietary purine** (*exogenous*);
     - ***Purine-Rich Foods***;
       - * ***High*** **purine foods include** (***avoid***);
         - **Organ meats**; Liver, kidneys, brain and heart.
         - **Game** (hunting) **meats**; rabbit and venison.
         - **Fish**; herring, mackerel, sardines and sprats.
         - **Seafood**; mussels, shellfish and caviar.
         - **Yeast extracts**; beer (not wine).
         - **High-fructose foods.**
       - * ***Moderate*** **purine foods** (***eat in moderation***);
         - **Meat**; beef, lamb chicken, pork.
         - **Poultry**; chicken and duck.
         - **Dried peas**, **beans** and **legumes**.
         - **Mushrooms**.
         - **Some vegetables**; cauliflower and spinach.
         - **Wholegrains**; bran, oatbran and bread.

- *N.B*; **Dietary purines** ***play an unimportant role*** in the ***generation*** of **hyperuricemia** in the ***absence*** of ***some derangement*** in **purine metabolism** or **elimination** (i.e. diet alone generally is not sufficient to cause hyperuricemia). ***However***, **diet modifications** are ***important*** for patients with **symptomatic hyperuricemia**.


Purine nucleotides (GMP, IMP, AMP)
5'-nucleotidase, adenosine deaminase and purine nucleoside phosphorylase
Purine bases (guanine and hypoxanthine)
Xanthine oxidase
Xanthine
Xanthine oxidase
Uric acid (elimination: one-third gastrointestinal tract, two-thirds renal)
Urate oxidase enzyme (absent in humans)
Allantoin (freely excreted product)

  2) **Increased purine nucleotide breakdown** (*endogenous*);
     - **Certain cancers** or **chemotherapy agents** (cellular destruction and tumor lysis syndrome).
  3) **Enzyme abnormalities** (*Genetic endogenous*);
     - ***Increase activity*** of **phosphoribosyl pyrophosphate (PRPP) synthetase.**
     - ***Deficiency*** of **hypoxanthine-guanine phosphoribosyltransferase (HGPRT).**
  4) **De novo synthesis of purine bases** (*endogenous*).

- ***Decrease*** **excretion of uric acid** ; (about 90% of cases)
  - *Approximately* **70%** of the **Uric Acid** ***produced*** **daily** is ***excreted*** by the **kidneys**, and the ***remainder*** is ***eliminated*** by the **intestines**.
  - ***Renal Handling of Urate***; **Uric Acid** → **Filtration** → **Reabsorption** → **Secretion** → **Postsecretory reabsorption.**
  1) ***Decrease*** **filtration**;
     - **Renal insufficiency.**
       - Chronic Kidney Disease (CKD).
  2) ***Decrease*** **secretion**;
     - **Patients** ***with acidosis***;
       - Diabetic ketoacidosis.
       - Ethanol.
       - Salicylate intoxication.
       - Starvation ketosis.
  3) ***Increase*** **reabsorption**;
       - Diuretic therapy.
       - Diabetes insipidus.


Filtration
100% filtered
99%
1%
50%
40%
Reabsorption
S1
Secretion S2
S3
Reabsorption
90%
10%
excreted

Renal Handling of Urate

- *Mixed type* (increase production and decrease excretion);
  1) **High Ethanol (alcohol) intake**;
     - *Increases* **production** by *increasing* **concentrations** of **Hypoxanthine** and **Xanthine**.
     - *Decreases* **excretion** by *promoting* **dehydration**.
     - *Decreases* **excretion** by *increasing production of* **Lactic Acid** (*acidosis*).
  2) **High dietary Fructose intake**;
     - *Increases* **production**; **Uric Acid** is one of the *products* of **Fructose** *metabolism*.
     - *Decreases* **excretion** by *competing* **Fructose** with **Uric Acid** for the **transport protein**.
  3) **Starvation**;
     - *Increases* **production**; **Body** *metabolize* its **own tissues** (purine-rich) *for energy*.
     - *Decreases* **excretion** by *competing* **Ketones** with **Uric Acid** for the **transport protein**.

➢ Gout Predisposing Factors (Risk Factors):-

- *Alcohol Consumption*;
  - **Beer** and **hard liquor** (*higher risk* of **incident gout** & *higher rate* of **gout flares**).
- *Dietary*;
  - ** *Avoid*;
    - **Organ meats**; Liver, kidneys, brain and heart.
    - **Game** (hunting) **meats**; rabbit and venison.
    - **Fish**; herring, mackerel and sardines.
    - **Seafood**; mussels, shellfish and caviar.
    - **High-fructose drinks or foods.**
  - ** *Limit*;
    - **Meat**; beef, lamb chicken, pork.
    - **Poultry**; chicken and duck.
    - **Dried peas, beans** and **legumes**.
    - **Mushrooms**.
    - **Some vegetables**; cauliflower and spinach.
    - **Wholegrains**; bran, oatbran and bread.

- *N.B*; **Dairy intake, folate intake** and **coffee consumption** (*not tea*) were each associated with *lower risk* of **incident gout** and in *some* cases *lower rate* of **gout flares**.

- *Drugs*;
  - **Thiazide** and **loop diuretics** (*higher risk* of **incident gout** & *higher rate* of **gout flares**).
  - *Low-dose* **Aspirin** (*may also* be a *risk factor* for gout).
  - **Xanthine oxidase inhibitors** (**XOIs**) and **uricosuric agents**; *only in initial therapy*.
- *Medical conditions*;
  - **Hyperuricemia**, **obesity**, **diabetes**, **hypertension**, **dyslipidemia**, **renal insufficiency** and **early menopause**.
- *Other conditions*;
  - **Trauma**, **surgery**, **starvation** and **dehydration**.
  - **Family history of gout**.

➢ Gout Symptoms and Signs:-

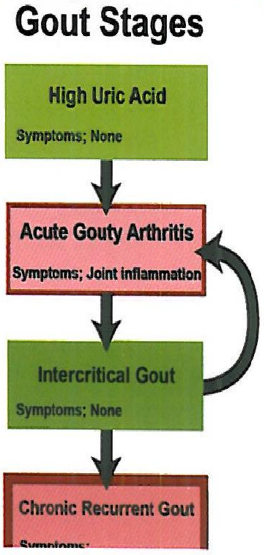
- **Fever**.
- *Intense* **pain**.
- **Erythema**.
- **Warmth**.
- **Swelling**.
- **Inflammation** of *involved joints*.

Uric acid crystals

➢ Gout Stages:-

- *Three stages of gout*:
  1) **Acute gouty arthritis**.
  2) **Intercritical gout**.
  3) **Chronic recurrent gout**.

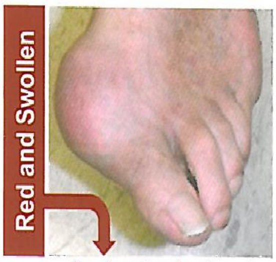
Gout is NOT gout until symptoms occur



- *Elevated* **Uric Acid** ***without* gout** or **kidney stone**, which has ***no symptoms***, is ***generally not treated***.
- ***Gout Stages*** (or ***Phases***);
  1) **Acute Gouty Arthritis**;
     - ***Reach*** its **peak 12-24 hours *after*** onset, ***without treatment*** takes ***approximately* 7-14 days**.
     - ***Symptoms***; Fever, pain, erythema, warmth, swelling & inflammation.
  2) **Intercritical Gout** (***time between attacks***);
     - **Person *feels* normal (*no symptoms*) *but*** is at **risk for recurrence**.
  3) **Chronic Recurrent Gout**;
     - ***Deposits*** of **hard lumps** of **Uric Acid** in the ***tissues*** (called; **tophi**), *may cause* **joint destruction**.
     - ***Decreased* kidney function** and ***increase* kidney stones (nephrolithiasis)**.
     - ***Frequent attacks*** and often a ***degree of* pain *even between* attacks**.

➢ Location of Gout Attacks:-

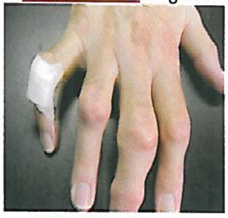
- ***Most common*** in the **big toe** (1st metatarso-phalangeal joint).
- ***Common*** in the **mid-foot**, **ankle** and **knee**.
- ***If untreated***, **multiple joints** (**fingers** and **wrists**).



Acute attack of gout

➢ Location of Gout Tophi:-

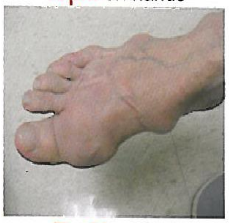
- **Tophi** can be found in ***numerous* locations**, ***especially*** on the **feet** and **elbows**; *other joints such as*
  - **Large joints** (knee, ankle, wrist, elbow, hip and shoulder).
  - **Medium joints** (wrist, ankle and elbow).
  - **Small joints** (interphalangeal).



Tophi on hands

➢ Severities of Chronic Tophaceous Gouty Arthropathy (CTGA):-

- **Mild**; **One joint** (stable disease).
- **Moderate**; **Two** to **four joints** (stable disease).
- **Severe**; **A)** ***More than* four joints** (stable disease).
  B) One or **more joints**, (unstable disease).

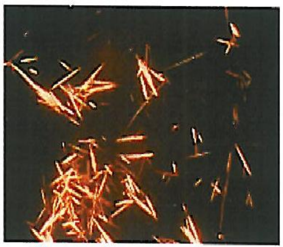


Tophi on foot

➢ Diagnosis of Gout:-

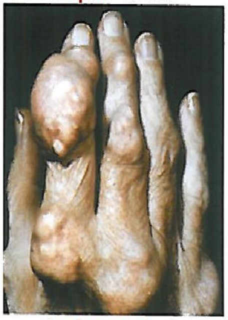
American College of Rheumatology Diagnostic Criteria

- ***Ideally***; by **Joint Fluid Test**;
  - Made by using needle to draw fluid from affected joint.
  - Examined under the microscope to identifying uric acid crystals in joint fluid or in tophus.

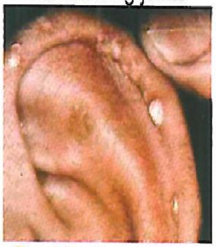


Monosodium urate crystals
crystals under polarizing light microscopy (needle-shaped or rods)

- ***Or***, ***presence*** of **6** or ***more*** of the following (***If joint aspiration is not possible***);
  1) ***More than* one attack** of **acute arthritis**.
  2) **Inflammation *reaches a maximum*** *within* **one day**.
  3) **Attack of arthritis** in a ***single joint***.
  4) **Joint *redness***.
  5) ***Unilateral*** 1st metatarsophalangeal joint (**big toe**) ***attack***.
  6) ***Unilateral* tarsal joint *attack***.
  7) **Uric Acid *elevation*** on **blood testing** (***Hyperuricemia***);
     - It may be difficult during an initial **acute attack** (serum uric acid may be low during flares), ***Best time*** is **2 weeks *after*** a **flare**.
  8) **Tophus** (***proven*** or ***suspected***).
  9) **X-ray** *shows* ***asymmetric*** **swelling within a joint**.
  10) **X-ray** *shows* **subcortical cyst *without* erosions**.
  11) **Joint fluid** is ***tested for*** **infection** and is ***negative***.



Large **tophaceous** deposits surrounding joints



Tophi at helix of ear.

Uric Acid Nephrolithiasis

- **Uric Acid** is ***unionized*** (*less soluble*) in **acidic medium** (pH = > 5.5), when **acidic urine** is ***saturated*** with **Uric Acid**, *spontaneous* ***precipitation*** of **stones** may occur.
- **Kidney stones** (**uric acid nephrolithiasis**) occurs in **10-25%** of ***patients with*** **gout**.
- The ***primary treatments*** are to **alkalinize**; **Potassium Citrate** (Uralyt-U®) and **dilute** (large water intake) **urine**.

➢ **Treatments:-**

- **Treatment Goals**;
  1) ***Serum urate target***: *Minimum* is ***less than*** **6 mg/dL**.
  2) ***Serum urate target***; ***less than*** **5 mg/dL** *may be needed to* ***improve*** **gout signs** and **symptoms** (or *if* **tophi present**).
  3) ***Decrease*** **frequency** of **acute gouty attacks**.
- **Treatment Options**;

Non-pharmacological Therapy

- **Dietary Modifications** (*see risk factors*);
  - **Vegetables** and **low-fat** or **nonfat dairy products** *should be* **encouraged**.
- **Maintaining adequate fluid intake.**
- **Weight loss** (*if obese*).
- **Exercise** (regular aerobic exercise program).
- **Smoking cessation.**

Pharmacological Therapy

Drugs for Gout Attacks

Acute Attacks of Gout

- ***For most patients***, **acute attacks of gouty arthritis** ***treated successfully*** with **short courses** of;
  1) **Nonsteroidal Anti-inflammatory Drugs (NSAIDs)**.
  2) **Colchicine**.
  3) **Corticosteroids** (oral, intramuscular or intra-articular routes).
- ***Treatment Steps*** (*2012 American College of Rheumatology Guidelines for Management of Gout*);
  A) ***Assess*** **severity of gouty attack**.
  B) ***Select*** **treatment according to severity**;
    * *For* ***mild*** to ***moderate*** **pain** (one or a few small joints or one or two large joints);
      - **Monotherapy** (**NSAIDs** or **colchicine** or **oral corticosteroid "OCS"**);
        - ***No preference*** **for one choice** ***over*** **another**.
        - **Intra-articular corticosteroid (ICS)** *used if* ***one*** or **two large joints**.
        - ***Single-dose*** **IM corticosteroid** (**Triamcinolone**) *may be* **used** ***followed by*** an **OCS**.
    * For ***severe pain*** or **polyarticular attack** (multiple large joints are affected);
      - **Combination therapy** (**NSAID + Colchicine** or **OCS + Colchicine**);
        - **Intra-articular corticosteroid (ICS)** *may be* **used** in *some* **patients**.
        - **NSAID + OCS** = ***synergistic*** **GI toxicity**.
  C) ***Onset***; **treatment** ***should be*** **start** ***within*** **24 hours** of **symptom onset** (***only*** **Colchicine** ***within*** **36 hours** of **attack** ***onset***).
  D) ***Continue*** **acute treatment** ***until*** the **gouty attack** has ***resolved*** (generally within 5-8 days).
  E) ***If*** **inadequate response** (response < 20% improvement in pain score within 24 hours, or <50% improvement in pain score ≥ 24 hours after initiating pharmacologic therapy);
    - *Switching* to ***another*** **monotherapy**.
    - Or ***add*** a ***second*** **agent**.
    - *If resistant*; ***use of*** a **biologic Interleukin-1 (IL-1)** ***inhibitor*** (**Anakinra** 100 mg SC daily for 3 days).
  F) ***Educate*** **patients** to ***can initiate*** **treatment** for **acute gouty attacks** on ***their own***.

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

Indomethacin (Indocid®)	**Naproxen** (Aleve®)	**Sulindac** (Clinoril®)

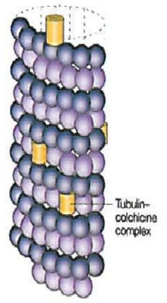
- **NSAIDs** are the ***first-line treatment of*** **acute gouty attacks.**
- There is *little* (*no strong*) **evidence** to **support** *one* **NSAID** as being ***more efficacious*** *than* **another.**
- **Indomethacin** has been ***historically favored*** as the **NSAID** of ***choice for*** **acute gout flares.**
- ***Only*** **FDA-approved**; **Indomethacin**, **Naproxen** and **Sulindac** for the ***treatment of*** **acute gouty attacks, BUT** ***other*** **NSAIDs** *may be* as **effective.**
- **Celecoxib** (Selective COX-2 inhibitor) is an ***option*** in ***certain patients*** with ***contraindications*** or ***intolerance*** to **NSAIDs.**
- ***Common Side Effects***; **GIT** (gastritis and bleeding), **kidneys** (renal dysfunction), **CVS** (risk of CV events in susceptible patients and hypertension).
- ***Dose*** (*continue full dose until attack completely resolves*);
  - **Naproxen**: 750 mg initially, followed by 250 mg 3 times daily.
  - **Naproxen ER**: 1000–1500 mg once daily, followed by 1000 mg once daily.
  - **Indomethacin**: 50 mg 3 times daily until pain tolerable, then reduce dose until attack resolves.
  - **Sulindac**: 200 mg twice daily.
  - **Ibuprofen**: 800 mg 4 times daily.
  - **Ketoprofen**: 75 mg 4 times daily. - **Piroxicam**: 20 mg once daily.
  - **Celecoxib**; 800 mg once, followed by 400 mg on day 1, then 400 mg twice daily for 1 week.

See previous chapter for full NSAIDs illustration

- **Dose** are ***reduced*** in **patient** ***with*** **renal** or **hepatic impairment.**
- ***Consider*** **co-administration** with a **proton-pump inhibitor** (**PPI**) for ***patients*** at ***risk for*** **gastrointestinal bleeding.**

Colchicine

- **Colchicine** [KOL-chi-seen], is an ***antimitotic drug***, is a ***plant alkaloid***, ***used for*** the ***treatment of*** **acute gouty attacks** and **familial Mediterranean fever (FMF).**
- **Colchicine** ***relieves*** the **pain** and **inflammation** of **gouty arthritis** in **12–24 hours** *without* ***altering*** the **metabolism** or **excretion** of **urates** and *without* ***other analgesic*** **effects** (***not an analgesic***).
- **Colchicine** is used ***less often than*** **NSAIDs**, and *may be* reserved as a **second-line therapy** when **NSAIDs** are ***contraindicated*** or ***ineffective.***
- ***Mechanism of action***; **Colchicine** *binds to* **micro-tubular intracellular protein** called **tubulin** *causing* its ***depolymerization***; lead to;
  - ***Inhibition*** of **cell division.**
  - ***Inhibition*** of **leukocytes migration.**
  - ***Prevention*** of **phagocytosis.**



- ***Side Effects***;
  - ***Dose-dependent GI side effects***; **nausea**, **vomiting** and **diarrhea** (about 50% to 80% of patients).
  - ***Chronic use***; **myopathy, neutropenia, aplastic anemia** and **alopecia.**
- ***Dose***; ***Recently***, **lower dose of colchicine** are used; **1.2 mg**; ***then*** **0.6 mg 1 hour** *later*; ***then*** **0.6 mg** ***once*** or ***twice*** **daily** ***until*** **attack resolves** (**Colchicine** **was** used in **higher doses**, ***hourly*** **dosing** *until* **gastrointestinal symptoms** ***become develops*** such as **diarrhea**).
- ***Contraindications***; ***Co-administration*** of **Colchicine** with ***strong*** **CYP3A4 inhibitors** (**Erythromycin** or **Clarithromycin**) in **renal** or **hepatic impairment** (***fatal toxicity has occurred***).

FDA Warning

- **Dose** ***should be reduced*** if ***co-administration*** of **Colchicine** with ***strong*** **CYP3A4 inhibitors** in ***normal*** **renal** or **hepatic function.**
- **Colchicine** ***should be*** **used carefully** for **patients** *with* **renal** or **hepatic** ***impairment*** with dosing repeated ***no more than*** **once** ***every*** **2 weeks** (Patients undergoing dialysis should receive a reduced dose of 0.6 mg, administered as a one-time dose only).

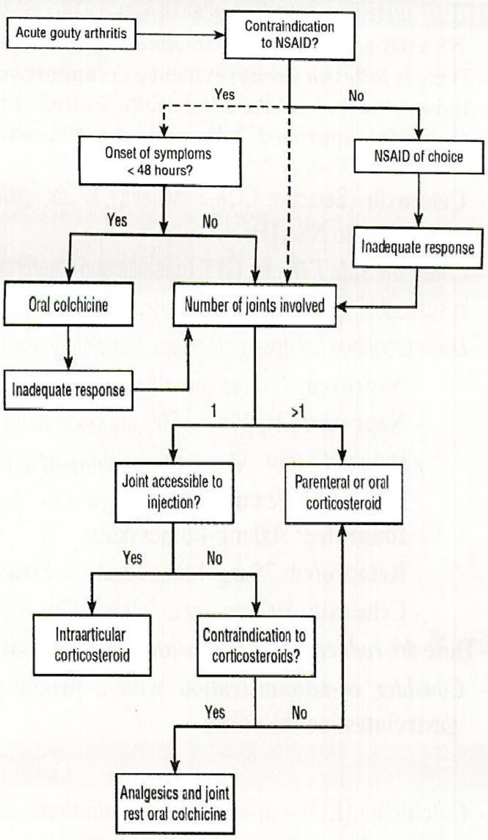
Corticosteroids (CSs)

- **Corticosteroids** *may be* an *appropriate alternative* for **patients** who *cannot* **tolerate NSAIDs** or **Colchicine**, *however*, *recent* evidence *indicates* that **corticosteroids** are *equivalent to* **NSAIDs** in the *treatment* of **acute gout flares**.

1) **Oral corticosteroid (OCS)** *used for all* cases of gout (oral route is a *first-line*);
    - **Prednisone** 0.5 mg/kg (30-60 mg) per day for 5–10 days.

      OR (*to reduce the risk of a rebound flare*), **Prednisone** 0.5 mg/kg for 2–5 days, then *tapered gradually* over 10 to 14 days, then discontinue (i.e.; 40 mg for 4 days, then 20 mg for 4 days, then 10 mg for 4 days).
    - **Methylprednisolone Dose Pack**; Six days of pre-dosed 4 mg package.
2) **IM corticosteroid**;
    - *Single dose* of **Triamcinolone** (60 mg) *followed by* **OCS** (*as above*).
3) **Intra-articular corticosteroid**;
    - **Triamcinolone** is *limited to* **one** or **two large joints**;
        - *Dose based on the size of the joint*;
            - **Large joint**; 40 mg of **Triamcinolone**.
            - **Medium joint**; 30 mg of **Triamcinolone**.
            - **Small joint**; 10 mg of **Triamcinolone**.

- *N.B.*; **Intra-articular corticosteroids** can be **used in *combination with* OCSs, NSAIDs** or **Colchicine**.


Acute gouty arthritis
Contraindication to NSAID?
Yes
No
Onset of symptoms < 48 hours?
NSAID of choice
Yes
No
Inadequate response
Oral colchicine
Number of joints involved
Inadequate response
1
>1
Joint accessible to injection?
Parenteral or oral corticosteroid
Yes
No
Intraarticular corticosteroid
Contraindication to corticosteroids?
Yes
No
Analgesics and joint rest oral colchicine

Algorithm for acute gouty arthritis (*DiPiro pharmacotherapy 8th*)

Drugs for Gout Prevention and Hyperuricemia

Urate-Lowering Therapy (ULT)

Hyperuricemia Treatment AND Gout Prevention

- ***Treatment Steps*** (*2012 American College of Rheumatology Guidelines for Management of Gout*);

A) ***Indications***; for **Urate-Lowering Therapy (ULT)**; ***should be*** **initiated** to ***prevent*** **recurrences** in persons *with*;

1) *History of gout at least* **two flares** *per* **year**.
2) *History of gout at least* **one** *per* **year** in *patient with* **chronic kidney disease** (≥ stage 2).
3) *History of gout with* **tophi**.
4) *History of gout* with *history* of **nephrolithiasis**.

   "even if the serum uric acid concentration is normal or only minimally elevated"

B) ***Initiation***;

1) **First-line ULT**; **Allopurinol** or **Febuxostat** (**Xanthine Oxidase Inhibitors; XOIs**).
2) ***Alternative* first-line ULT**; **Probenecid** (**Uricosuric**); ***If*** **XOIs** is **contraindicated** or **not tolerated**.

** **Use of anti-inflammatory for acute gout (NSAIDs, Colchicine** or **OCS)** ***with*** or ***just before*** **ULT** in ***all*** **patients**; to prevent risk of acute gouty attacks during initiation of ULT; Rapid decrease in urate concentrations after ULT initiation, resulting in remodelling of articular urate crystal deposits and acute flare may occur.

1) **Oral** ***low-dose*** of **Colchicine** is a ***first-line*** **option**;
    - 0.6 mg once or twice daily (don't forget warning/contraindication/dose adjustment).
2) ***Low-dose*** of **NSAIDs** is an ***alternative first-line*** **option**.
    - **Naproxen**; 250 mg twice daily.
    - **Indomethacin**; 25 mg twice daily.
3) ***Low-dose*** of **OCSs**; if **Colchicine** and **NSAIDs** are ***contraindicated***, ***not tolerated***, or ***ineffective***; **Prednisone** or **Prednisolone**; ≤10 mg daily.

C) ***Goal***; **Treatment with ULT** ***until achieve*** **serum urate target**;
- Monitor serum urate every 2–5 weeks;
    1) ***Serum urate target***: *Minimum* is ***less than*** **6 mg/dL**.
    2) ***Serum urate target***; ***less than*** **5 mg/dL** *may be needed to* ***improve*** **gout signs** and **symptoms** (or *if* tophi present).

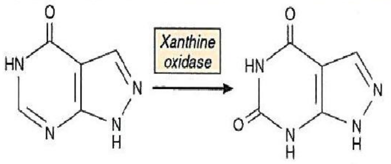
D) ***Continue***; **ULT** ***should be continued after*** **urate** has been ***achieved*** at the **target level** and ***there*** have been **no attacks** of ***gout for*** **3–6 months**.

E) ***Monitoring***; **After goal is** ***achieved***, ***continue*** **monitoring** ***every*** **6 months**.

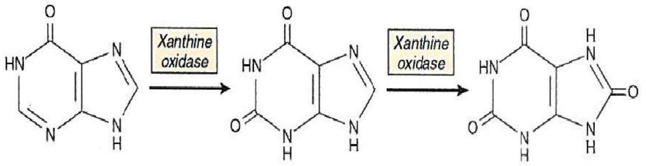
Xanthine Oxidase Inhibitors (XOIs)

Allopurinol (Zyloric®) (Zyloprim®)

- **Allopurinol** [al-oh-PURE-i-nole], a ***xanthine oxidase inhibitor***, is a ***purine analog***.
- The *structure* of **Allopurinol**, an ***isomer*** of **Hypoxanthine**.
- ***Like*** **Uric Acid**, **Allopurinol** is ***metabolized by*** **xanthine oxidase**, but the ***resulting*** compound, **Alloxanthine**.



Allopurinol Alloxanthine



Hypoxanthine Xanthine Uric acid

Pharmaco Kinetics

- ***Absorption***; ***Completely*** **absorbed** after oral administration.
- ***Metabolism***; ***Primary*** **metabolite** is **Alloxanthine (Oxypurinol)**.
- ***Half-life***; ***Long*** **half-life, once-daily** *dosage*.
- ***Excretion***; **Urine** and **feces**.

Mechanism OF Action

- **Allopurinol** ***decrease*** **Uric Acid production** by ***competitively inhibiting*** **xanthine oxidase** ***enzyme*** (*due to structure similarity*) in the ***last*** **two steps** in **Uric Acid** ***biosynthesis***.

- ***Indications***; **Urate-lowering therapy** in the ***treatment of*** **gout** and **hyperuricemia** ***secondary to*** **chemotherapy**.

Dose

- ***Starting Dose***; ***should be no greater than*** **100 mg**/day (50 mg/day in patients with stage 4 chronic kidney disease);
    - ***Reduces*** **early gout flares** and ***risk*** of **hypersensitivity syndrome**.
- ***Dose Titration***; ***gradually titrate*** dose **every 2–5 weeks** to appropriate **maximum dose** (800 mg daily with normal renal function) or ***until*** **goal urate level reached**.
- ***Maintenance Dose***; can be ***higher than*** **300 mg daily**, even in CKD, as long as **patient is educated** and ***regular monitoring*** for **hypersensitivity, rash, pruritus and elevated hepatic enzymes**.

Side Effects

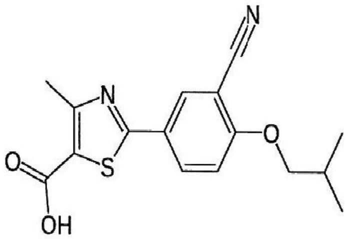
- *About* **20% of patients** on **Allopurinol** report ***side effects***;
  - *GI Side Effects*; **Nausea, vomiting**, and **diarrhea.**
  - ** **Allopurinol hypersensitivity syndrome (AHS)**; *Mortality; 20–25%.*
    - ***Severe*** **hypersensitivity reactions;**
      - **Urticaria.**
      - *As well as* **Stevens-Johnson syndrome.**
      - **Hepatotoxicity.**
      - **Eosinophilia.**

Drug Interactions

- **Allopurinol** interferes with the metabolism of **6-mercaptopurine**, **Azathioprine** and **Theophylline**, requiring a ***reduction*** in **dosage** of ***these* drugs** (approximately one-third to one-fourth).

Febuxostat (Uloric®) (Feburic®)

- **Febuxostat** [feb-UX-oh-stat], a ***xanthine oxidase inhibitor***, is ***structurally unrelated*** to **Allopurinol.**
- *Mechanism*; *Selective* **direct non-competitively blocking** the *active site* of **xanthine oxidase.**
- *Approval*; **Febuxostat** was ***first approved*** in **2009.**
- **Febuxostat VS Allopurinol;**
  - *Similarity*;
    - ***Same*** **indications** and **drug interactions.**
    - ***Same*** **Pregnancy category; C.**
  - *Differences*;
    - *Cost*; **Febuxostat** more expensive.
    - *Mechanism*;
      - **Allopurinol; Competitive inhibition.**
      - **Febuxostat; Non-competitive inhibition.**
    - *Side effects*; **Allopurinol** more severe.
    - CKD; **Allopurinol** require dose adjustment.



- *Dose*;
  - **Febuxostat** is *approved at doses* of 40, 80 or 120 mg.
  - *Starting dose*: 40 mg once daily.
  - ***If goal serum urate not reached***; dose may increase dose to 80 mg once daily.
- *N.B.*; Use with caution in severe renal impairment (CrCl <30 mL/minute); insufficient data.
- *Finally*; **Febuxostat** and **Allopurinol** are ***equally effective*** in ***preventing* recurrent gout.**

Uricosuric Agents

- *Uricosuric Agents*; are **substances** that *increase* the **excretion** of **Uric Acid** in the ***urine***.

Probenecid

Sulfinpyrazone (Anturane®)

- **Probenecid** [proe-BEN-a-sid] and **Sulfinpyrazone** [sul-fin-PEER-a-zone] are a ***uricosuric drugs***.
- *Mechanism*; *increase* the **excretion** of **Uric Acid** in the *urine* by ***inhibiting*** postsecretory renal proximal tubular **reabsorption** of **Uric Acid.**
- **Probenecid** it *was used* (World War II) to ***increase* blood levels** of **Penicillin** (decreased excretion).
- *Indications*; ***If* XOIs is *contraindicated* or *not tolerated*.**
- *Dose*;- **Probenecid**; *Initial*; **250 mg *twice*** a **day** for **1-2 weeks** and then **500 mg *twice*** a **day** for **2 weeks** (when initiating, increase fluid intake or urine alkalinization).
  - **Sulfinpyrazone**; *Initial*: 100-200 mg *twice*, *with* **meals** or **milk**, ***gradually* increasing *when* necessary** to ***full* maintenance dosage** (200-400 mg *twice*) **in 1 week.**
- *Most Common Side Effects*; **GI disturbances.**
- *Contraindications*; **Probenecid *contraindicated*** in **patients** *with* **CrCl *less than*** 50 mL/min.
- *Drug Interactions*;
  - **Probenecid *blocks* tubular secretion** of **Penicillin** and other **β-lactam antibiotics**. It also ***inhibits excretion*** of **Methotrexate, Naproxen, Ketoprofen, Indomethacin, Acyclovir** and **other drugs**.
  - **Sulfinpyrazone *increase toxicity of*** **Salicylates, Paracetamol, Warfarin** and **Tolbutamide.**
- **Secondary Uricosurics** *(second-line)*; **Losartan** and **Fenofibrate** *(off-label use)*.

Selective Uric acid Reabsorption Inhibitor (SURI)

Lesinurad (Zurampic®)

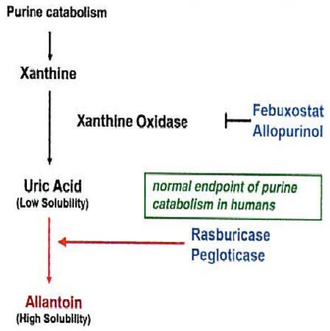
- **Lesinurad** [le-SIN-ure-ad] is a *first **Selective Uric acid Reabsorption Inhibitor** (**SURI**)*.
- ***Approval***; *FDA* approval on December, 2015. ***European Union*** on February 2016.
- ***Mechanism***;
  - It acts by ***inhibiting*** the **uric acid transporter 1 (URAT1)**, which is ***responsible for*** the ***majority*** of the **renal reabsorption** of **Uric Acid**.
  - It also ***inhibits*** **organic anion transporter 4** (OAT4), a **Uric Acid** ***transporter associated with*** **diuretic-induced hyperuricemia**.
- ***Indications***; In ***combination with*** a **xanthine oxidase inhibitor (XOI)** for the ***treatment of*** **hyperuricemia** ***associated with*** **gout** in ***patients*** who have ***not achieved*** **target serum uric acid levels** with a **xanthine oxidase inhibitor** ***alone*** [NOT USED ALONE].
- ***Recommended Dose***; **200 mg once daily** in ***combination with*** a **xanthine oxidase inhibitor**, including **Allopurinol** or **Febuxostat**.
- ***Side Effects***; **Headache, influenza,** ***increase*** **serum creatinine level**, and **gastroesophageal reflux disease** (GERD); ***more frequent*** when **used alone** ***without*** **XOIs**.
- ***Contraindications***; - **Severe renal impairment** (CrCl less than 30 mL/min).
  - **Tumor lysis syndrome** or **Lesch-Nyhan syndrome**.
- ***FDA WARNING***; - **Renal events** (**acute renal failure** ***more common*** when **used alone** ***without*** **XOIs**).
  - **Cardiovascular events**.

Recombinant Urate Oxidase (UO) "Uricase"

- **Urate Oxidase** (**UO**) ***enzyme*** or **Uricase**, is ***absent*** in **humans** (found nearly all organisms except humans) and ***catalyzes*** the ***oxidation*** of **Uric Acid** ***to*** **Allantoin**.
- **Allantoin** is an ***inactive*** (nontoxic) and ***more soluble*** **metabolite** and ***easily*** **excreted**.

Pegloticase (Krystexxa®)

- **Pegloticase** [peg-LOE-ti-kase] is a **Polyethylene Glycol** ***conjugate*** with ***recombinant urate oxidase enzyme***.
- ***Approval***; **US FDA** ***approved*** in **2010**.
- ***Indications***; ***treatment of*** **severe, refractory** or **resistant chronic gout** (serum uric acid levels have failed to normalize and signs and symptoms are inadequately controlled with xanthine oxidase inhibitors at maximum appropriate dose or xanthine oxidase inhibitors are contraindicated; an option for about 3% of patients).
- ***Dose***; 8 mg IV infusion every 2 weeks.



FDA Warning

- **Anaphylaxis** and **infusion reactions**; life-threatening allergic reactions.
- ***Should be administered*** in **healthcare settings** by **rheumatologist**.
- **Patients** ***should be pre-medicated*** with **antihistamines** & **corticosteroids**.
- ***Life-threatening*** **hemolysis** in ***patients with*** **glucose-6-phosphate dehydrogenase (G6PD) deficiency**.

Rasburicase (Elitek®)

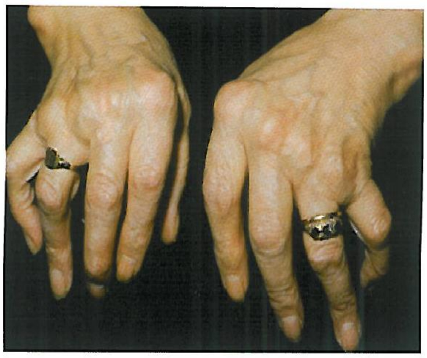
- **Rasburicase** [ras-BURE-i-kase] is a ***recombinant urate oxidase enzyme***.
- ***Approval***; **US FDA** ***approved*** in **2009**.
- ***Indications***; ***Prevention*** and ***treatment*** of **hyperuricemia** ***caused by*** **Tumor Lysis Syndrome (TLS)**, in ***people receiving*** **chemotherapy** for **hematologic cancers** such as **leukemias** and **lymphomas**.
- ***Dose***; 0.2 mg/kg as a 30-minute IV infusion once a day for up to 5 days.

FDA Warning

- **Anaphylaxis**.
- ***Life-threatening*** **hemolysis** in ***patients with*** **glucose-6-phosphate dehydrogenase (G6PD) deficiency**.
- *It has been associated with* **methemoglobinemia**.

Rheumatoid Arthritis (RA)

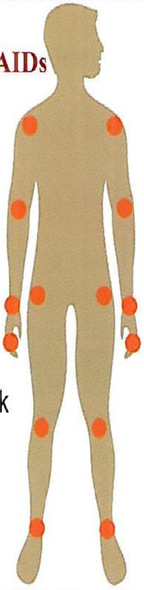
➢ Overview:-



- **Rheumatoid Arthritis** (**RA**); is the ***most common*** **autoimmune inflammatory** (***chronic***) **arthritis** in **adults**, ***characterized by symmetrical inflammation of*** **joints** and ***may involve*** **other organ system** (*immune system mistakenly attacks body's tissues*).
- The **cause** of **rheumatoid arthritis** is ***not clear*** and ***unknown***.
- **Treatment** *focuses on* is *decrease* **inflammation** and **pain**, *decrease* **disease progression** as well as *managing* **symptoms** and *preventing* **joint damage**.
- **Disease-modifying antirheumatic drugs** (**DMARDs**) or **biologic agents** ***should be*** **started** ***after*** **diagnosis** of **RA**.
- *Analgesics* and *anti-inflammatory* **drugs** such as; **corticosteroids** and **NSAIDs** are ***frequently used*** to help to *control* **symptoms**.

➢ Prevalence:-

- *Globally*; **RA** *affects approximately* **1% of adults**.
- *In 2005*, an estimated **1.5 million** (**0.6%**) of **US adults**.
- *About* **3 cases** *per* **10,000 population** were *diagnosed with* **RA** *annually*.
- It ***can*** **occur** at *any age*, but the ***incidence*** are ***increasing*** *with* **age** (peaking between; 35 & 50 years).
- **Women** are affected **3 times** ***more than*** **men** (not in older age).
- *Approximately* **40% of patients** ***become*** **disabled** *after* **10 years** (reduce work hours, loss of job and unable to find a job).

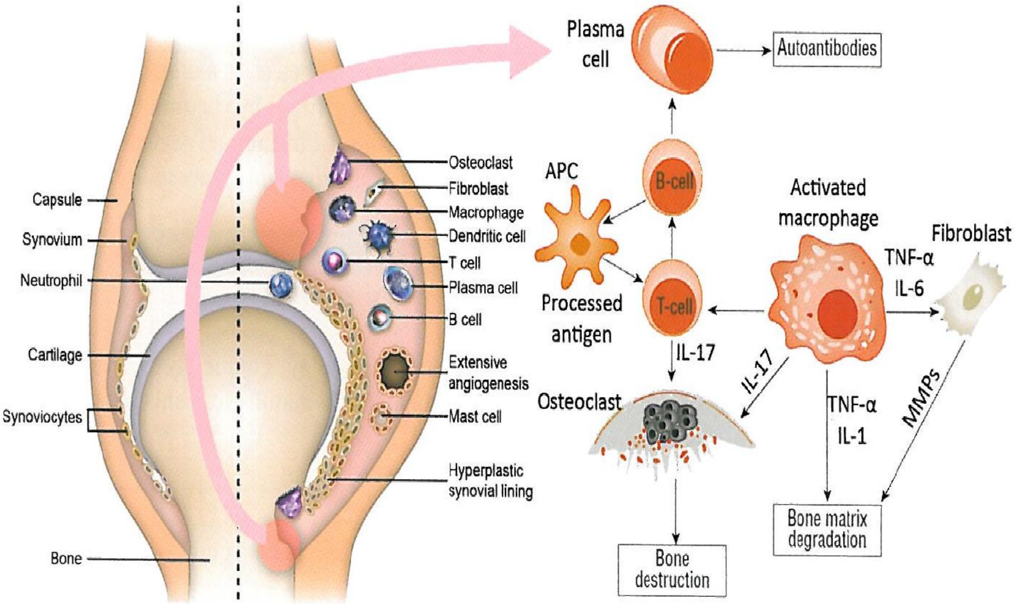


Joint involvement in RA

➢ Causes:-

- The *cause* of **RA** is ***unknown***.
- **Genetic**, **environmental**, **hormonal**, **immunologic** and **infectious** ***factors*** may ***play*** **significant roles**.
- **Psychological** and **lifestyle factors** (***smoking tobacco***) *may* **influence disease** ***development***.

➢ Pathophysiology:-

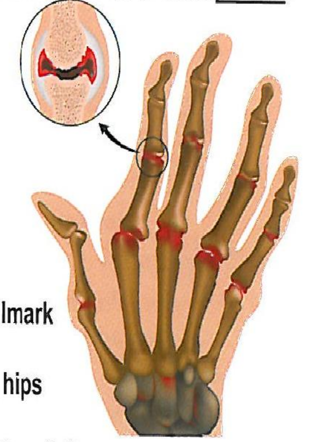

Capsule
Synovium
Neutrophil
Cartilage
Synoviocytes
Bone
Osteoclast
Fibroblast
Macrophage
Dendritic cell
T cell
Plasma cell
B cell
Extensive angiogenesis
Mast cell
Hyperplastic synovial lining
Plasma cell
Autoantibodies
APC
B-cell
Processed antigen
T-cell
IL-17
Osteoclast
Bone destruction
Activated macrophage
Fibroblast
TNF-α
IL-6
IL-17
TNF-α
IL-1
MMPs
Bone matrix degradation

APC; antigen-presenting cell, MMP; matrix metalloproteinase, IL; interleukin, TNF-α; tumor necrosis factor α

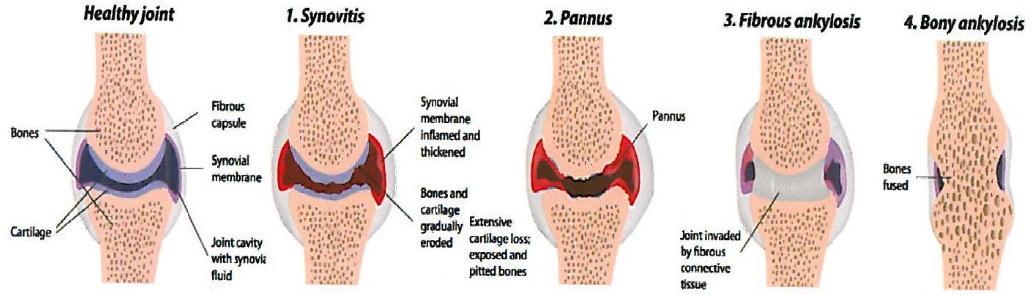
- **Pathophysiology** of **RA** is ***not* completely understood**.
- ***Both* genetic** and **environmental factors** (**cigarette smoking**, **infection** or **trauma**) are ***trigger*** that sets off an **autoimmune reaction**, *leading to* **chronic joint inflammation**.
- ***Pathologic hallmark***;

  1) Inflammation (**synovitis**). **2) Cartilage Destruction.** **3) Bone Erosion.**
  - **Macrophages *migrate to*** *affected* **synovium**; *leading to* **local immune *reaction*** in the **tissue**.
  - ***Activated* T-cells** (*mainly* CD4) with **macrophages** *produce* ***pro-inflammatory* cytokines** and **chemokines** (e.g. tumor necrosis factor α [TNF-α], granulocyte-macrophage colony-stimulating factor [GM-CSF], various interleukins [ILs] and interferon-γ).
  - **Plasma cells** *derived from* **B lymphocytes** *produce* **autoantibodies** known as **rheumatoid factors** (**RF**) and **anticyclic citrullinated peptide antibody** (**anti-CCP**); N.B.; destructive arthritis can occur in absence of autoantibodies.
  - ***Chronically***; the **synovial lining cells** *produce* **various materials**, which contribute to **cartilage destruction**, **osteoclast-mediated bone absorption** (**bone destruction**), **synovial inflammation** and **prostaglandins** (mediate pain and inflammation).
  - They also can ***stimulate* fibroblasts** which ***produce* matrix metalloproteinases**, which contribute to **bone matrix destruction**.
  - The ***inflamed***, ***proliferating* synovium** characteristic of **rheumatoid arthritis** is called ***pannus***.
  - **Fibrin deposition**, **fibrosis** and **necrosis** are ***also present***.

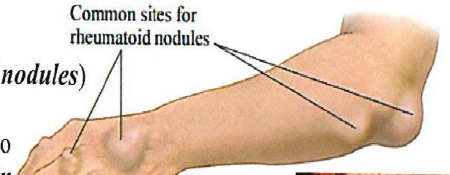
➢ Signs and Symptoms:-

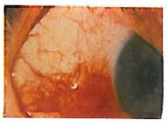


- ***Before joint symptoms*** (*in most patients with RA*);
  Low-grade fever, **malaise**, **arthralgias**, **loss of appetite** (*lead to weight loss*) and **weakness**.
- ***Joint symptoms*** (***symmetrically***); **pain**, **swelling**, **stiffness**, **redness** and **warmth**;
  - **Persistent symmetric** (*same joints on both sides of the body*) **polyarthritis** (*multiple joint synovitis*) of **hands** and **feet**; is a **hallmark feature**.
  - **Symptoms** often ***spread to*** the **wrists**, **knees**, **ankles**, **elbows**, **hips** and **shoulders**.
  - **Joint stiffness** that is ***usually* worse** in the **mornings** and ***after* inactivity**, **gentle movements** *may* ***relieve* symptoms** in **early stages** (*these signs help distinguish* **rheumatoid** *from* **osteoarthritis**).
  - **Joint deformity** is *generally seen* ***late*** in the **disease**.


Healthy joint
1. Synovitis
2. Pannus
3. Fibrous ankylosis
4. Bony ankylosis
Bones
Cartilage
Fibrous capsule
Synovial membrane
Joint cavity with synovia fluid
Synovial membrane inflamed and thickened
Bones and cartilage gradually eroded
Extensive cartilage loss; exposed and pitted bones
Pannus
Joint invaded by fibrous connective tissue
Bones fused

- ***Extra-articular manifestations***; **RA *primarily affects* joints**, but it *also affects* **other organs** in ***more than* 15-25%** of ***individuals***.
  - **Skin**:
    - ***Most common***; **Rheumatoid nodules** (***SC* nodules**) (20% of patients).
    - Typically affect the **limbs**, but they *can* also *affect* the **entire body** and may ***arise within*** the **lungs** or **heart**.


Common sites for rheumatoid nodules



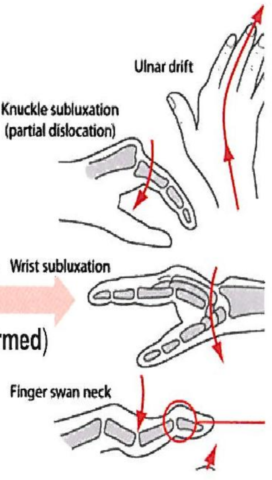
  - **Ocular**:
    - ***Most common***; **keratoconjunctivitis sicca** (***secondary* Sjögren's syndrome**, 10% of patients), **scleritis**, and **rheumatoid corneal melts**.

- **Oral**:
  - **Oral dryness** and **salivary gland swelling** (*secondary* **Sjögren's syndrome**).
- **Pulmonary**:
  - **Pleural disease** is *most common* but *usually* **asymptomatic.**
  - **Rheumatoid lung nodules** are **common** and *usually* **asymptomatic.**
  - *Increase incidence* of **pulmonary toxicity** in ***patients treated*** with **Methotrexate** & **Leflunomide**.
- **Cardiac**:
  - *More prone to* **atherosclerosis** and *risk of* **myocardial infarction**.
  - **Pericarditis** is the *most common.*
  - **Endocarditis**, **valvulitis** and **fibrosis** has been *observed.*
- **Blood Vessels**:
  - **Vasculitis** (invasion of blood vessel walls by inflammatory cells) usually is seen in patients with long-standing RA.
- **Renal**: (rare)
  - **Renal amyloidosis** is *most common* **renal manifestation** of **RA** (a soluble proteins "amyloid fibrils" aggregate and deposit extracellularly in tissues causing organ dysfunction, the kidney is one of the most frequent sites).
  - **Glomerulonephritis** and **interstitial renal disease** are *uncommon.*
- **Splenic**:
  - **Felty's syndrome**; **splenomegaly**, **neutropenia** (*recurrent infections*) and **hepatomegaly.**
- **Hematological**: **Anaemia** is one of the *most common* **extra-articular manifestation** of **RA.**
- **Neurological**:
  - **Carpal tunnel syndrome** (**CTS**) is ***most common*** (caused by compression of the median nerve by swelling around the wrist).
  - **Peripheral neuropathy** may occur.

➢ Diagnosis:-

- **History**; *hallmark feature*;
  - *Persistent* **symmetric polyarthritis** (*synovitis*).
- **Physical Examination**; *Assess the following*;
  - **Joint symptoms** (*symmetrically*);
    - **Pain, swelling, stiffness, redness & warmth.**
    - **Deformity**

    (**X-rays** of the **hands** and **feet** are *generally* **performed**)
  - **Extra-articular manifestations.**
  - **Rheumatoid nodules.**



- **Blood Tests**;
  - **Rheumatoid factor** (**RF**) *antibody*;
    - **Sensitivity**; high (60-70% of patients with RA).
    - **Specificity**; low; (RF is also seen in other illnesses,
      for example Sjögren's syndrome,
      hepatitis C, systemic lupus erythematosus,
      chronic infections and in approximately 10% of the healthy population).
    - **Normal range**; < 20 u/ml.
  - **Anti-Cyclic Citrullinated Peptide** (**Anti-CCP**) *antibody or* **Anti-Citrullinated Protein Antibodies** (**ACPA**);
    - **Sensitivity**; low (50-85%). **Specificity**; high (90–95%). **Normal range**; < 20 u/ml.
  - **Erythrocyte Sedimentation Rate** (**ESR**);
    - Not specific for RA and there are many factors that can interfere with the results.
  - **C-Reactive Protein** (**CRP**); Not specific for RA.
  - **Complete Blood Count** (**CBC**);
    - Help to inform patient health, often RA patients reveal a mild to moderate normocytic-normochromic anemia (related to inflammatory disease activity as an anemia of chronic disease).

- **Diagnostic Criteria**; [*2010 American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) Diagnostic Criteria*];
  - * Point value between 0 and 10.
  - * Score of 6 or greater classifies a person with a diagnosis of rheumatoid arthritis.

  A) **Joint involvement** (swelling or tenderness upon examination);
  - 1 large joint = 0 points.
  - 2-10 large joints = 1 point.
  - 1-3 small joints (with or without involvement of large joints) = 2 points.
  - 4-10 small joints (with or without involvement of large joints) = 3 points.
  - More than 10 joints (at least 1 small joint) = 5 points.

  B) **Serology Test** (at least 1 test result is needed for classification);
  - Negative RF and negative anti-CCP = 0 points.
  - Low-positive RF or low-positive ACPA = 2 points.
  - High-positive RF or high-positive ACPA = 3 points.

  C) **Acute-Phase Reactant Test** (at least 1 test result is needed for classification);
  - Normal C-reactive protein (CRP) and normal ESR = 0 points.
  - Abnormal CRP or abnormal ESR = 1 point.

  D) **Duration of Symptoms** (synovitis);
  - < 6 weeks = 0 points.
  - ≥ 6 weeks = 1 point.

➢ Disease Activity:- (*2012 ACR Disease Activity Measures*);

* The ACR has endorsed 6 recommended measures for RA disease activity to facilitate clinical decision making in practice.

* The 6 measures result in a single continuous index with defined ranges for;

- **Low disease** ***activity*.**
- **Moderate disease** ***activity*.**
- **High disease** ***activity*.**
- **Clinical remission.**

* For more detailed information on how to use these tools and how to calculate the measurement tools, *see the* "2012 Rheumatoid arthritis disease activity measures: American College of Rheumatology Recommendations for use in clinical practice".

➢ Managements:-

- **Goals**; There is ***no cure* for RA**, *__but__* ***treatments can***;
  - **Minimize symptoms** (pain and swelling).
  - **Prevent bone deformity.**
  - **Maintain day-to-day functioning.**
- **Options**;
  - ***Optimal care*** consists of an integrated approach that includes ***__both__*** **pharmacologic** and **non-pharmacologic** ***therapies*.**

Non-pharmacological Therapy

There are a wide variety of non-pharmacological therapies available

- **Education and counseling**; Can help to better understand the nature of RA and cope with the challenges of this condition.
- **Smoking and alcohol**; Smoking is a risk factor for rheumatoid arthritis and alcohol consumption may increase the risk of liver damage from some RA drugs such as Methotrexate.
- **Rest**; Inflamed joints should be rested, but physical fitness should be maintained as much as possible.
- **Exercise**; inactivity can lead to a loss of joint motion, contractions, and a loss of muscle strength.
- **Physical and occupational therapy**; helping people with RA to be able to continue to normal activity.
- **Nutrition and dietary therapy**; people with active RA sometimes lose their appetite, dietary therapy helps to ensure eat an adequate amount of calories and nutrients.
- **Massage**; can help to facilitate and restore movement and function.
- **__Surgery__**; patients with ***__end-stage__*** rheumatoid arthritis may have pain due to joint damage, surgery may be recommended to replace a damaged joint.

Pharmacological Therapy

- **RA Medication Summary:-**

A) **NSAIDs** and/or **Corticosteroids** may be ***used for*** **symptomatic relief** *if needed*.

B) **Disease Modifying Antirheumatic Drugs** (**DMARDs**) [dee-MAAR-D];

1) **Non-biologic DMARDs**;
   - ***Most common***; **Methotrexate**, **Leflunomide**, **Hydroxychloroquine** and **Sulfasalazine**.
   - ***Less common***; *such as*; **Gold Salts**, **Azathioprine**, **Cyclosporine** and **D-Penicillamine**.

2) **Biologic DMARDs**;
   - ***TNF inhibitors***; **Etanercept**, **Adalimumab**, **Infliximab**, **Certolizumab** & **Golimumab**.
   - ***Non-TNF Biologic***; **Abatacept**, **Rituximab**, **Anakinra**, **Tocilizumab** and **Tofacitinib**.

C) **Tetracyclines**; **Minocycline** (*has anti-inflammatory effects*).

- **NSAIDs** and **Corticosteroids** have a ***short onset*** of **action** while **DMARDs** can take ***several weeks*** or ***months*** to ***demonstrate*** a **clinical effect**.
- **Fast-acting *agents*** can be ***reduced*** in **dose** or ***discontinued*** with ***successful*** **DMARD therapy**.

Fast-acting Agents

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

- **NSAIDs** have ***no impact*** on ***disease progression***, **NSAIDs** ***interfere with*** **prostaglandin** ***synthesis*** through ***inhibition*** of the **cyclooxygenase** (**COX**) ***enzyme***, thus ***reducing*** **pain** and **inflammation**.
- **NSAIDs** possess *both* **analgesic** and **anti-inflammatory** ***properties*** and ***reduce*** *stiffness associated* with **RA**.
- **NSAIDs** ***should be used with caution*** in ***those with*** **gastrointestinal**, **cardiovascular**, or **kidney problems**.
- **COX-2 inhibitors** (such as **Celecoxib**), and **NSAIDs** are ***equally effective***.

See previous chapter for full NSAIDs illustration

Corticosteroids

- **Corticosteroids** are ***used in*** **RA** for their ***anti-inflammatory*** and ***immunosuppressive*** **properties**.
- **Corticosteroids** *commonly used* in **RA** to bridge the time until DMARDs become effective (*This is termed* **bridging therapy**).
- **Oral corticosteroid** (**OCS**) are ***typically*** **used**;
  - **Prednisone** **10 mg/day**, but ***some*** **patients** may ***require*** even **higher dosages**.
  - **Methylprednisolone**; can be used.
- **IM corticosteroid**; may be ***preferable in some*** **patients**.
- **Intra-articular**; may be ***preferable in some*** **patients**, it is associated with the fewest number of systemic adverse effects.
- **Corticosteroids side effects** ***associated with*** **long-term steroid use**, *include*;
  - **Hypothalamic-pituitary–adrenal** ***suppression***, **Cushing's syndrome**, **osteoporosis**, **myopathies**, **glaucoma**, **cataracts**, **gastritis**, **hypertension**, **hirsutism**, **electrolyte imbalances**, **glucose intolerance**, **skin atrophy**, and ***increased susceptibility*** to **infections**.

Slow-acting Agents

Disease Modifying Antirheumatic Drugs (DMARDs)

- **DMARD** ***should be started within*** the ***first* 3 months** of ***symptom onset***.
- ***Early treatment with*** **DMARDs** ***results*** in a ***more* favorable outcome**.
- ***Early treatment with*** **DMARDs** can ***reduce* mortality**.

Non-biologic (Traditional) DMARDs

Methotrexate (Methotrexate®)

- **Methotrexate** [meth-oh-TREX-ate] (**MTX**) is a ***synthetic antimetabolite*** (**Folic acid *antagonist***).
- It was ***originally used as*** a **chemotherapy *treatment for*** **cancer** (first made in 1947), ***used in much lower doses*** for **rheumatoid arthritis** and *other* **rheumatic diseases** (such as systemic lupus erythematosus and Sjögren's syndrome).
- *In* **RA MTX** works to ***reduce* inflammation** and to ***decrease* joint damage**.
- In **psoriatic arthritis MTX *not only*** **treats** the **joint symptoms *but also improves*** the **skin disease**.
- **MTX *now considered*** the ***first-line* DMARD** for ***treatment of*** **rheumatoid arthritis**.
- **MTX** may be ***combined with other*** **DMARDs** or ***with*** a **biologic agent** if **MTX** alone ***does not* adequately control a patient's disease**.

Pharmaco Kinetics

- ***Absorption***; *approximately* **70% absorbed** after **oral administration**.
- ***Protein bound***; **50%**.
- ***Metabolism***; by **liver** and **intracellularly**.
- ***Half-Life***; - **low-dose**; 3-10 hr. - **High-dose**; 8-15 hr.
- ***Excretion***: **Urine** (80-100% within 24 hr), **feces** (small amounts).

Mechanism OF Action

1) ***For cancer*** (***folic acid antagonist*** or ***folate analogue***);
   - ***Due to structure similarity*** (**Folic acid** and **MTX**); **MTX *competitively inhibits*** **dihydrofolate reductase (DHFR)**, an enzyme *responsible for* ***convert*** **Folate** to active **Tetrahydrofolate**.
   - **Folate** is ***essential for*** **purine** and **pyrimidine base *biosynthesis***, so ***synthesis*** *will be* **inhibited**.
   - **MTX**, *therefore*, ***interferes with*** **DNA synthesis**, **repair** and **cellular replication** (*impair cancer cells growth*).
2) ***For rheumatoid arthritis*** (*the exact mechanism is unknown*);
   - ***Anti-inflammatory effects*** of *low dose* **MTX**;
     - *Inhibit* **purine metabolism**, leading to ***accumulation*** of **intracellular adenosine** which is a ***potent inhibitor*** of **inflammation**, as a result; ***suppress*** **inflammatory functions** of **neutrophils, macrophages, dendritic cells** and **lymphocytes**.
     - **MTX** may ***diminish*** **inflammation** in the joint is by ***diminishing*** **cytokine production (Interleukin-1)**.

- **MTX** *was known as* **Amethopterin**; is an ***antineoplastic antimetabolite*** with ***immunosuppressant properties***.

Therapeutic Uses

- ***Cancer Chemotherapy***;
  - **MTX** is an ***antimetabolite*** used in the *treatment of* ***certain* cancers**.
- ***Autoimmune Diseases***;
  - **MTX** is used as a ***disease-modifying agent*** for *some* **autoimmune diseases**, including; **rheumatoid arthritis, juvenile dermatomyositis, psoriasis, psoriatic arthritis, lupus, sarcoidosis, Crohn's disease**.
- ***Abortion***; US FDA pregnancy **category X**.
  - **MTX** is an ***abortifacient agent*** during the ***early stages***, *generally* in ***combination with*** **Misoprostol**.
  - It is also ***used to treat*** **ectopic pregnancies**.

Dose

- **MTX** may be given **IM, SC** or **orally**.
- ***Dosing regimen for*** the treatment of **RA 7.5-15** mg ***once*** a **week**.
- ***Onset of effect***; *within* **3-6 weeks** of ***starting*** **treatment**.

- ***N.B***; *Doses of* **MTX** *required for* **RA** treatment are ***much lower*** **than** those needed in **cancer chemotherapy** and are given ***once*** a **week**, *thereby* ***minimizing* adverse effects**.

Side Effects

- *Most common side effects*; **Mucosal ulceration** and **nausea**.
- *Other side effects*; **leukopenia, anemia, stomatitis, GI ulcerations** and **alopecia** (*due to inhibiting cellular proliferation*), **halitosis** (bad breath odour).
- *Dose-related side effects*; **hepatotoxicity**.
- *Rare side effects*; **acute pneumonitis** and **kidney failure**.
- *Monitoring*; **Liver enzyme tests, complete blood counts**, and **monitoring** ***for*** **signs of infection** are recommended.

- *Taking* **Folinic acid** (leucovorin®) **24 hours** ***after each*** **weekly dose** or by the use of ***daily*** **Folic acid** (not in the same day; *off-days*), although this may *decrease* the **efficacy** of the **Methotrexate** by about 10%, ***but*** this *reduces* the *severity* of **adverse effects**.
- **N.B.**; **Folinic acid** ***should be distinguished from*** **Folic acid**. **Folinic acid** ***does not*** **require** the action of **dihydrofolate reductase** for its *conversion*.
- **Levoleucovorin** (Fusilev®) is an **enantiomerically** ***active form*** of **Folinic acid**.

Drug Interactions

- **Penicillins** (decrease elimination of **MTX**), **Aminoglycosides** (reduce GI absorption of **MTX**), **Probenecid** (inhibits **MTX** excretion) and **NSAIDs** with high doses of **MTX** (by PP displacement; elevate level and prolong **MTX**).
- **Retinoids** & **Trimethoprim** (may potentiate hepatotoxicity & hematotoxicity)
- **Cyclosporine** (may potentiate hematologic toxicity).
- **Nitrous oxide** (may potentiating the haematological toxicity).
- **Omeprazole** and **Valproate** (may increase the plasma **MTX** level).
- **Caffeine** *may* antagonise the effects of **MTX** on rheumatoid arthritis by antagonising the receptors for adenosine.

Leflunomide {Original brand (Arava®)} {Egypt brand (Avara®)}

- **Leflunomide** [le-FLOO-noe-mide], ***like* MTX**, is an ***immunomodulatory non-biologic*** **DMARD**.
- Arava® was developed by Sanofi Aventis and approved by the US FDA in 1998.
- **Leflunomide** has ***efficacy similar to*** **MTX** for *treating* **RA**.

Pharmaco Kinetics

- *Absorption*; ***completely*** **absorbed** after **oral administration**.
- *Protein bound*; **>99%**.
- *Metabolism*; by **GI mucosa** and **liver** to ***active metabolite*** (**A77-1726** or **Teriflunomide**).
- *Half-Life*; ***very long*** **18–19 days**.
- *Excretion*: **Urine** (43%) and **feces** (48%) (**Cholestyramine** may be used to rapidly clear the drug).

Mechanism OF Action

- The ***active metabolite*** (**Teriflunomide**) ***inhibits*** **dihydroorotate dehydrogenase** (**DHODH**) ***enzyme*** (a mitochondrial enzyme involved in de novo pyrimidine synthesis), ***inhibits*** **pyrimidine synthesis,** ***leading to*** a *decrease* in **lymphocyte** *proliferation* and *modulation* of **inflammation** (the mechanism is not been fully determined).

- **Teriflunomide** was approved by the FDA in 2012 for the ***treatment of patients with*** **relapsing forms of multiple sclerosis** (**MS**) (see page no 348).

Therapeutic Uses

- **Leflunomide** is ***approved for*** the treatment of **RA**.
- It can be used as ***monotherapy*** or in ***combination with*** **MTX**.
- *Dose*;
  - *Loading dose*: **100 mg** orally *once* a **day** for **3 days**.
  - *Maintenance*: **20 mg** orally *once* a **day** (If not well tolerated "signs of dose-related toxicity" the dose may be decreased to 10 mg orally once a day).
- *Onset of effect*; ***relatively rapid*** *within* **4-8 weeks**.

Side Effects

- *Most common side effects* (up to 10%); **Respiratory infection, diarrhea, nausea, headache, hypertension, alopecia, rash, weight gain,** and ***abnormal*** **liver function tests**.
- *Monitoring*; signs of infection, complete blood counts and liver enzymes.

- ***Pregnancy***; **category X** (**Leflunomide** and **Teriflunomide**);
  - Women should wait to become pregnant for at least 2 years after discontinuation of treatment and plasma levels of A771726 should be less than 0.02 mg/L).
  - ***Or*** Administer **Cholestyramine** 8 grams, 3 times daily for 11 days, verify plasma levels less than 0.02 mg/L by 2 separate tests at least 14 days apart. If plasma levels are higher than 0.02 mg/L, additional **Cholestyramine** treatment should be considered.
  - Men who are planning parenthood and are being treated with Leflunomide should undertake **Cholestyramine** washout and wait for at least one and possibly three spermatic cycles before inseminating their spouse.

Hydroxychloroquine (Plaquenil®)

- **Hydroxychloroquine** [hye-drox-ee-KLOR-oh-kwin] is an ***antimalarial drug***.
- The ***mechanism*** of the **anti-inflammatory action** in **rheumatic diseases** is ***unclear***.
- ***Onset of effects***; **6 weeks** to **6 months** (> 6 months without a response = therapeutic failure).
- **Hydroxychloroquine** is ***partially metabolized*** in the **liver** and is ***excreted*** by the **kidney**.
- ***Main advantage***; ***less toxicities*** on the **liver**, **kidney** and **immune system** than *other* **DMARDs**, which *simplifies* **monitoring**.
- **Hydroxychloroquine** is very ***extensively*** **tissue-bound**, particularly in ***melanin-containing*** **tissues** such as the **eyes** (**OCULAR TOXICITY**).
- ***Dose*** in **RA**; Oral: 200-300 mg twice daily, after 1–2 months may to 200 mg twice or once daily.
- ***Most common side effects***; **GI effects**; *mild* **nausea**, **dyspepsia**, and **diarrhea** (can be managed by taking doses with a food or a glass of milk). ***Chronic use side effects***; **skin pigmentation**, **hair bleaching**, **alopecia skin rash** and **CNS disturbances**.

** ***Serious side effects***; ***Ocular toxicity***; accommodation defects, benign corneal deposits, blurred vision, scotoma (small areas of decreased or absent vision in the visual field) and night blindness.

** ***Monitoring***; Ophthalmoscopy every 9–12 months and Amsler grid test at home every 2 weeks.

- ***Contraindications***; ***Patients with***;
  - **G6PD deficiency** (or ***hypersensitivity*** to **4-aminoquinoline** ***derivatives***).
  - **Retinal** or **visual field changes** *due to* **4-aminoquinoline** ***derivatives***.
  - ***Long-term therapy*** in **children**.
- **N.B.**; **Chloroquine** is ***another antimalarial agent*** that is also ***sometimes*** **used**.

Sulfasalazine (Azulfidine®)

- **Sulfasalazine** (**SSZ**) [SUL-fa-SAL-a-zeen] is a ***prodrug***, is a ***sulfa drug*** *cleaved by* **bacteria** in the **colon** into **Sulfapyridine** and **Mesalazine** (**5-Amino-Salicylic Acid**; **5-ASA**).
- **Sulfapyridine** is *probably* the ***active moiety*** in ***treating*** **RA** (**unlike inflammatory bowel disease**, **Mesalazine** (Pentasa®) is the ***active moiety*** in treating this disease, see page no 559).
- The ***exact mechanism*** of **Sulfasalazine** in ***treating*** **RA** is ***unknown***.
- ***Both*** **Sulfasalazine** and its ***metabolites*** are ***excreted in*** the **urine**.
- ***Onset of effects***; takes **1-3** (> 3 months without a response = therapeutic failure).
- ***Dose*** in **RA**; **500 mg** to **1 g** ***twice daily***.
- ***Use*** of **Sulfasalazine** is *often* ***limited*** by its **adverse effects** (These can be minimized by gradually increasing doses and in dividing doses, or use enteric coated formulations or administration with meals).
- ***Most common side effects***; **nausea**, **vomiting**, **headache** and **rash**.
- ***Other side effects***; **anemia** and **methemoglobinemia** and *reversible* **infertility in men**.
- **Sulfasalazine** may cause the **patient's urine** and **skin** to turn a **yellow-orange color**.
- ***Pregnancy***; **Category B**.
- ***Contraindications***; **G6PD deficiency**, or ***hypersensitivity*** to **sulfa drugs** and **urinary obstruction**.
- ***Drug interactions***; **Warfarin** and **oral hypoglycemic** (plasma protein displacement). **Sulfasalazine** ***absorption decreased***; **antibiotics** (destroy the colonic bacteria) and **iron supplements**.

Recommendations

(2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis)

- **MTX** ***should be*** the ***preferred initial*** **DMARD** for **most patients**.
- ***In patients*** who have **hepatitis B** or **C**; **using DMARDs** ***other than*** **MTX** or **Leflunomide**, ***such as*** **Sulfasalazine** or **Hydroxychloroquine**.
- **Hydroxychloroquine** is *sometimes* ***combined with*** **Methotrexate** for ***additive benefits*** or as part of a regimen of "**triple therapy**" with **Methotrexate** and **Sulfasalazine**.

Other Non-biologic DMARDs

Gold Salts	**Cyclophosphamide** (Cytoxan®) (Endoxan®)
Chlorambucil (Leukeran®)	**Azathioprine** (Imuran®)
Cyclosporine (Sandimmune Neoral®)	**D-penicillamine** (Artamin®)

- ***Although*** **these drugs** can be ***effective***, **BUT** they are **used** ***less frequently*** **today** *because of* **toxicity**, ***lack of*** **long term benefit** or **both**.
- **Gold Salts**;
  - ***Mechanism***; in **RA** is ***unknown***.
  - ***Administration***; By **IM injection** (can also be administered orally but low efficacy).
  - ***Onset of effect***; **3-6 months**.
  - ***Toxicity***; **Acute renal failure** & **skin pigmentation** (***Chrysiasis***; blue-grey to greyish purple)
- **Cyclophosphamide** [SYE-kloe-FOS-fa-mide];
  - ***Class***; ***Alkylating Agent*** (***Chemotherapy Drug***).
  - ***Uses***; **Certain cancers** and **autoimmune diseases**.
  - ***N.B.***; it **remains an important treatment in autoimmune diseases**, it ***reserved for*** **severe, refractory rheumatoid arthritis** (in case of failure of other DMARDs).
  - ***Side effects***; **Nausea**, **vomiting**, ***increased risk of***; **developing certain cancers** and **risk** of **infections**, **anemia** (bone marrow suppression), **alopecia** and **infertility** (in males and females).
- **Chlorambucil** [klor-AM-bue-sil];
  - ***Class***; ***Alkylating Agent*** (***Chemotherapy Drug***).
  - ***Uses***; **Certain cancers** and **autoimmune diseases**.
  - ***Side effects***; **Nausea**, **vomiting**, ***increased risk of***; **developing certain cancers** and **risk** of **infections**, **anemia** (bone marrow suppression), **alopecia** and **infertility** (in males and females).
- **Azathioprine** [AY-za-THYE-oh-preen];
  - ***Class***; ***Immunosuppressive Drug***.
  - ***Uses***; **Organ transplantation** and **autoimmune diseases**.
  - ***Side effects***; **Nausea**, **vomiting**, **hepatitis**, **pancreatitis**, ***increased risk of***; **infections** & **developing certain types of cancers**.
- **Cyclosporine** [SYE-kloe-SPOR-in];
  - ***Class***; ***Immunosuppressive Drug***.
  - ***Uses***; **Organ transplantation** and **autoimmune diseases**.
  - ***Side effects***; **Nausea**, **vomiting**, **hepatitis**, **pancreatitis**, ***increased risk of*** **infections**.
- **D-Penicillamine** [D-PEN-ih-SILL-ah-meen]; is ***d-isomer*** of ***amino acid metabolite*** of **Penicillin**, with ***no antibiotic*** **properties**.
  - ***Class***; ***Chelating Agent*** (Chelates gold, copper, mercury and arsenic).
  - ***Uses***; **Wilson disease** (accumulation of copper in tissues) and **rheumatoid arthritis**.
  - ***Side effects***; **Nausea**, **vomiting**, **diarrhea** and **bone marrow suppression**.

➢ Tetracyclines:-

- The ***tetracycline derivative*** **Minocycline** has been suggested as a treatment alternative for patients with **RA** who have ***low disease activity*** and ***without*** **features of poor prognosis**, ***dose*** of **Minocycline** in **RA** is 100–200 mg daily.

Biologic DMARDs

- **Biologic DMARDs** are *genetically engineered* **protein molecules** that *block* the **proinflammatory cytokines**;
  1) **TNF-α Inhibitors**; **Etanercept**, **Infliximab**, **Adalimumab**, **Certolizumab** and **Golimumab**.
  2) **T-Cell Activation Blockade**; **Abatacept**.
  3) **B-Cell Depletion**; **Rituximab**.
  4) **IL-1 Inhibitors**; **Anakinra**.
  5) **IL-6 Inhibitors**; **Tocilizumab**.
  6) **Janus Kinase (JAK) Inhibitors**; **Tofacitinib**.

* ***These drugs*** may be *effective when other* **DMARDs** (non-biologic) ***fail*** to ***achieve*** **adequate responses** but are ***considerably*** **more expensive** ***to use***.

* ***Most*** of **these drugs** are ***increased*** an ***incidence*** of *risk of* **tuberculosis infection** (tuberculin skin testing is recommended).

* **Live vaccines** ***should not*** **be given** to *patients taking* **biologic agents** to ***avoid*** the **risk** of **infection**.

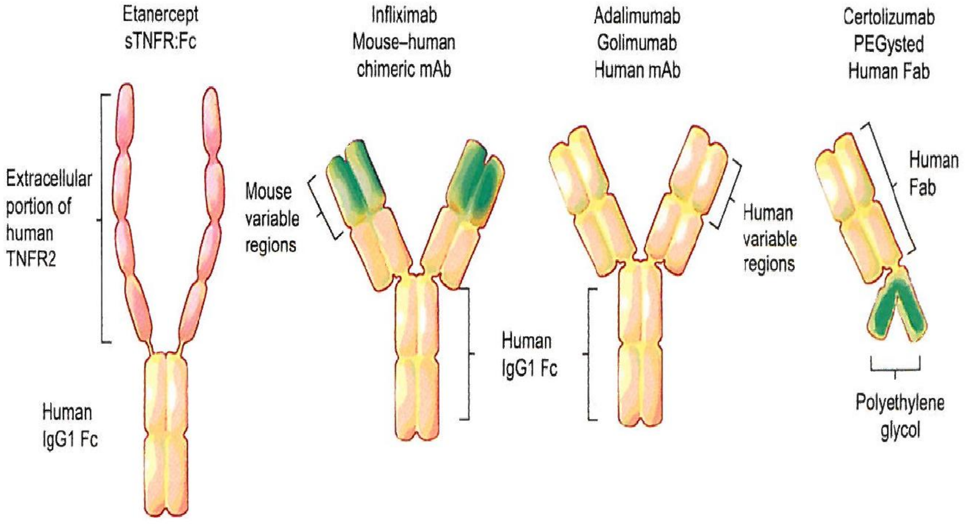
TNF-α Inhibitors

- **Tumor necrosis factor alpha (TNF-α)** is a ***pro-inflammatory cytokine*** *produced by* **macrophages** and **lymphocytes**. It is *found in* ***large quantities*** in the **rheumatoid joint**.
- **TNF** ***antagonists*** were the ***first*** of the **biological DMARDs** to be approved for the ***treatment*** of **RA**.
- **Anti-TNF agents** began to ***enter the market*** for **RA** in **1999**.
- There are ***currently*** **5 TNF inhibitors** FDA *approved for* the ***treatment*** of **RA**; listed in order of their approval for RA; **Etanercept**, **Infliximab**, **Adalimumab**, **Certolizumab** and **Golimumab**.

***Precautions*** or ***Contraindications***; for **anti-TNF agents**;

- ***Risk of*** **serious infections**, or ***history of*** **recurring infections**; **black box warning**.
- **Recent malignancies**; *especially* **lymphoproliferative cancer**; **black box warning**.
- **Congestive heart failure (CHF)**; New York Heart Association (NYHA) class III or IV heart failure
- **Demyelinating diseases**; *like* **multiple sclerosis**.
- ***Avoid*** **vaccination** *with* **live vaccines**.

- ***Response*** was seen in **60-75%** of **patients**.
- ***Onset of effect***; ***rapid onset of action*** sometimes with **improvements** seen ***within*** **2-4 weeks**, however, ***additional improvements*** can be seen ***over*** **3-6 months**.
- ***Pregnancy***; **category B**.
- The global market for TNF inhibitors in 2008 was $13.5 billion and $22 billion in 2009.


Etanercept
sTNFR:Fc
Infliximab
Mouse–human chimeric mAb
Adalimumab
Golimumab
Human mAb
Certolizumab
PEGysted
Human Fab
Extracellular portion of human TNFR2
Human IgG1 Fc
Mouse variable regions
Human IgG1 Fc
Human variable regions
Human Fab
Polyethylene glycol

Structures of Anti TNF α

Fc; complex immunoglobulin region

Etanercept (Enbrel®)

- **Etanercept** [ee-TAN-er-cept] is a ***recombinant, fully*** **human receptor *fusion* protein.**
- ***Mechanism***; **Etanercept** *consisting of two* **soluble *fully human* TNF p75 receptor moieties *linked to*** the **Fc portion** of **human IgG_1** (*see photo*); it ***binds*** **TNF-α molecules,** *making it* **biologically inactive**, this ***results in down-regulation*** of **macrophage** and **T-cell function.**
- ***Indications***; **RA, ankylosing spondylitis, psoriasis** and **psoriatic arthritis**.
- ***Dose***; **25 mg SC *twice*** **weekly** or **50 mg SC weekly**.
- **Methotrexate, Glucocorticoids** or **NSAIDs** ***may be*** **continued *during* treatment** (70% of patients taking **Etanercept** are also using **Methotrexate**).

** ***Precautions*** or ***Contraindications***; *increase risk for* **infections, malignancy** and **worsening heart failure** (**DON'T *forget*** the **anti-TNF precautions**; *see previous page*).

Infliximab (Remicade®)

- **Infliximab** [in-FLIX-i-mab] is a ***recombinant*** **DNA-derived chimeric human-mouse** (75% human, 25% mouse) **IgG_1 monoclonal antibody.**
- ***Mechanism***; **Infliximab *bind*** with **soluble TNF-α** (found in the blood and transmembrane in the outer membranes immune cells) and ***prevents*** its **interaction** with **TNF-α surface receptors** (p55 and p75), this ***results in down-regulation*** of **macrophage** and **T-cell function.**
- ***Indications***; **RA, Crohn's disease, ulcerative colitis, psoriasis, psoriatic arthritis** and **ankylosing spondylitis.**
- ***Dose***; 3–5 mg/kg IV at 0, 2, and 6 weeks, then every 8 weeks; may be increased to 10 mg/kg.
- ***N.B.***; The **immune system** in **patients** *treated with* **Infliximab *may develop* antibodies** to this ***foreign*** **protein** of **Infliximab** (*called* **anti-infliximab antibodies**), resulting in ***reduced*** **Infliximab *efficacy*.**
- **Methotrexate *should be*** **given** *as long as with* **Infliximab** to ***decrease*** or ***prevent*** the ***formation*** of **anti-infliximab antibodies.**
- **Infusion site reactions *may*** **occur** and may ***correlate with*** **anti-infliximab antibodies *formation*** (antihistamines may prevents some of these reactions).

** ***Precautions*** or ***Contraindications***; ***Like other*** **TNF-α blocking agents.**

Adalimumab (Humira®)

- **Adalimumab** [a-dal-AYE-mu-mab] is a ***recombinant fully*** **human IgG_1 monoclonal *antibody*.**
- ***Mechanism***; ***Like*** **Infliximab**, *but* **Adalimumab** is ***fully*** **human** (***not*** **chimeric**), ***no*** **foreign protein** in **Adalimumab**, is ***less antigenic than*** **Infliximab.**
- ***Indications***; **RA, Crohn's disease, ulcerative colitis, psoriasis, psoriatic arthritis** and **ankylosing spondylitis, hidradenitis suppurativa** and **juvenile idiopathic arthritis.**
- ***Dose***; ***usual dose*** is 40 mg **SC** every other week (14 days).

** ***Precautions*** or ***Contraindications***; ***Like other*** **TNF-α blocking agents** (*serious TB infection*).

Golimumab (Simponi®)

- **Golimumab** [goe-LIM-ue-mab] is a ***human*** **monoclonal antibody** with a ***high*** **affinity** for ***soluble*** and ***membrane-bound*** **TNF-α.**
- ***Indications***; **RA, ulcerative colitis, psoriatic arthritis** and **ankylosing spondylitis.**
- ***Dose***; - **Simponi®**; 50 mg **SC** monthly.
  - **Simponi®** Aria; 2 mg/kg IV infused over 30 minutes at weeks 0 and 4, then every 8 weeks.

** ***Precautions*** or ***Contraindications***; ***Like other*** **TNF-α blocking agents.**

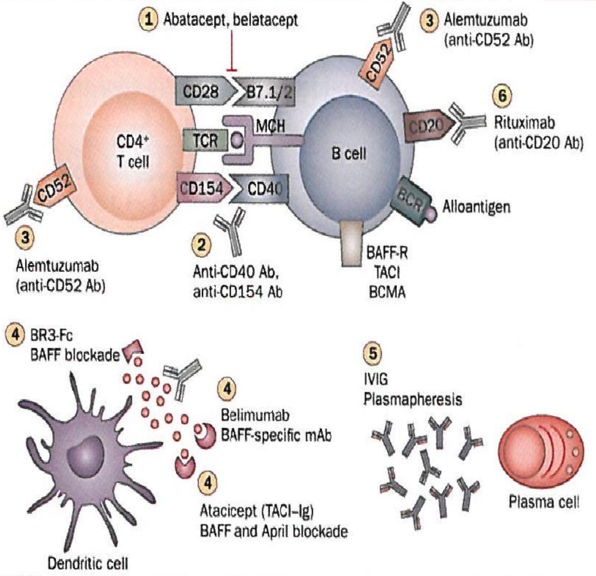
Certolizumab Pegol (Cimzia®)

- **Certolizumab** [ser-toe-LIZ-oo-mab] is a ***unique*** **TNF-α blocker** that contains a ***recombinant, humanized*** **antibody Fab fragment *conjugated to*** a **Polyethylene Glycol (PEG)** (not contain **IgG_1**) with ***specificity*** for ***human*** **TNF-α.**
- ***Indications***; **RA, Crohn's disease, psoriatic arthritis** and **ankylosing spondylitis.**
- ***Dose***; 400 mg **SC** initially and repeat at weeks 2 and 4, followed by 200 mg every other week or 400 mg every 4 weeks.

** ***Precautions*** or ***Contraindications***; ***Like other*** **TNF-α blocking agents.**

T-Cell Activation Blockade

- **T lymphocytes (CD4⁺ T *cells*)** need ***two* interactions** to *become activated*:
    1) The **antigen-presenting cell (macrophages** or **B cells)** must ***interact*** with the **receptor** on the **T cell**.
    2) The **CD80/CD86** (CD= Cluster of Differentiation) **protein** (*also known as* **B7-1** and **B7-2**) on the **antigen-presenting cell** ***must interact with*** the **CD28 protein** on the **T cell**.


① Abatacept, belatacept
③ Alemtuzumab (anti-CD52 Ab)
CD52
CD28
B7.1/2
MCH
TCR
CD4⁺ T cell
B cell
CD20
⑥ Rituximab (anti-CD20 Ab)
CD154
CD40
CD52
BCR
Alloantigen
③ Alemtuzumab (anti-CD52 Ab)
② Anti-CD40 Ab, anti-CD154 Ab
BAFF-R
TACI
BCMA
④ BR3-Fc BAFF blockade
⑤ IVIG Plasmapheresis
④ Belimumab BAFF-specific mAb
④ Atacicept (TACI-Ig) BAFF and April blockade
Plasma cell
Dendritic cell

Abatacept (Orencia®)

- **Abatacept** [a-BAT-ah-cept] is a ***soluble recombinant* fusion protein** *composed of* the **Fc region** of the **immunoglobulin IgG1** ***fused to*** the **extracellular domain** of CTLA-4 (**CTLA4-Ig**).
- **CTLA-4** (cytotoxic T-lymphocyte-associated protein-4), *also known as* **CD152** (cluster of differentiation 152); It acts as an "**off**" switch when bound to CD80 or CD86 on the surface of antigen-presenting cells.
- ***Mechanism***; **CTLA-4 (Abatacept)** has ***very high* affinity** for **CD28** on the T-cell surface, when **Abatacept *binds to*** **CD28** on the **T cell surface** (***second signal***), it ***prevents*** the **activation of T cells.**
- ***Indications***; ***Monotherapy*** (***first-line therapy***) or in ***combination*** (*not with other biologic drugs*) with *other* **DMARDs** in patients with ***moderate*** to ***severe*** **rheumatoid arthritis.**
- **Abatacept** may use in **autoimmune type 1 diabetes** to ***protect*** surviving **beta cells** from **autoimmune *attack***.
- ***Dose***; **IV infusion** based on patient weight (<60 kg; 500 mg. 60–100 kg; 750 mg. >100 kg; 1,000 mg) every 2 weeks for two doses after and then every 4 weeks.
- ***Pregnancy***; **category C**.
- ***Common side effects***; **headache, *upper* respiratory infections, nasopharyngitis** and **nausea.**
- **N.B.**; ***Concomitant use*** **Abatacept** with **anti-TNF-α** is ***not recommended*** due to the ***increased incidence*** of **serious infection.**

B-Cell Depletion

- **B cells** are an ***important*** **inflammatory cell** with ***multiple*** **functions** in the **immune *response***.
- They ***serve*** as **antigen presenting cells**, directly ***interact*** with **T-cells** and **others**, can ***secrete*** **cytokines**, and ***differentiate*** into **antibody-forming plasma cells.**

Rituximab (Rituxan®)

- **Rituximab** [ri-TUK-si-mab] is a ***genetically engineered chimeric*** (murine/human) **monoclonal antibody** directed ***against*** the **CD20 antigen** *found on* the ***surface*** of **normal** and **malignant B lymphocytes**, ***resulting*** in **B-cell depletion.**
- **Rituximab *was originally*** *developed to* treat **non-Hodgkin's lymphoma**.
- ***Indications***; **Hematological cancers, autoimmune diseases** and **organ transplantation**.
- ***Dose***; in **RA**; Two infusions of 1,000 mg are given 2 weeks apart. **Methylprednisolone** 100 mg should be given 30 minutes prior to reduce the incidence and severity of infusion reactions.
- ***Recommendations***; **Rituximab** is used in ***combination*** with **Methotrexate** in patients who ***failed to*** **one** or **more** ***types*** of **treatment** (***including anti-TNF***).
- ***Pregnancy***; **category C**.
- ***Common side effects***; **Infusion reactions** (urticaria, hypotension and angioedema).

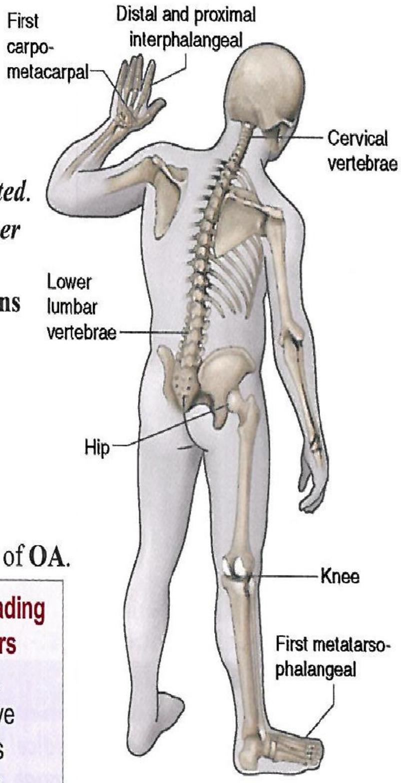
Osteoarthritis (OA)

➢ Overview:-

- **Osteoarthritis (OA)** is the ***most common* joint disease.**
- It is ***characterized by breakdown*** of the **cartilage, bony *changes*** of the **joints, *deterioration*** of **tendons** and **ligaments,** and ***various degrees*** of **inflammation** of the **joint lining** (***synovium***).
- **OA** is derived from the ***Greek* word** part **osteo-**, *meaning* "**bone**", combined with arthritis: **arthr-**, *meaning* "**joint**", and **-itis**, *meaning* "**inflammation**".
- The ***most common symptoms*** are **joint pain** and **stiffness.**
- ***Initially***, **symptoms occur *only following* exercise,** but ***over time*** may *become* **constant.**
- **OA *predominantly involves*** the **weight-bearing joints**, including the **knees, hips, cervical** and **lumbosacral spine & feet.**
- **OA *was previously considered*** a **wear-and-tear disease** (*i.e. damage from work or use*).

➢ Prevalence:-

- **OA** is the ***most common* articular disease.**
- ***Globally*** *approximately* **250 million** people have **knee osteoarthritis** (3.6% of population).
- **OA *affects from* 20-30 million *individuals*** in **US.**
- *Prevalence* of **OA increases *with* age;** ***more* 50%** of **adults *older than* 65 years** are ***affected.***
- ***Older than* 45 years,** the *prevalence* of **OA** is ***higher*** among **women** *than* among **men.**
- The disorder is ***more prevalent*** in **Native Americans** than in the ***general* population.**



Joint involvement in OA

➢ Risk Factors:-

- The **daily stresses *applied to*** the **joints,** *especially* the **weight-bearing joints, *play*** an ***important role*** in the ***development*** of **osteoarthritis.**
- **Joint vulnerability** and **joint loading** are the **two *major factors*** contributing to the ***development*** of **OA.**

Joint Vulnerability Factors

- Age, genetics, trauma and infection.
- Muscle weakness and crystal deposition.
- Disorders of bone and diabetes mellitus.
- Acromegaly.
- Previous inflammatory arthritis.
- Previous surgical procedures (e.g., meniscectomy).
- Heritable metabolic causes (e.g., alkaptonuria, hemochromatosis and Wilson disease).
- Changes in sex hormone levels.

Joint Loading Factors

- Obesity.
- Repetitive use (jobs requiring heavy labor and bending).

➢ Types:- There are *two* main types of OA, which have *differing* causes.

Primary (Idiopathic) Osteoarthritis

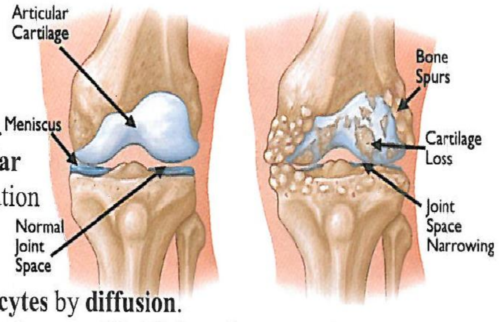
- It has ***no identifiable*** **cause**, the ***most common*** **type** and ***may associated*** with **aging.**
- ***Subclasses***; **localized** (affecting one or two sites) and **generalized** (affecting three or more sites).

Secondary Osteoarthritis

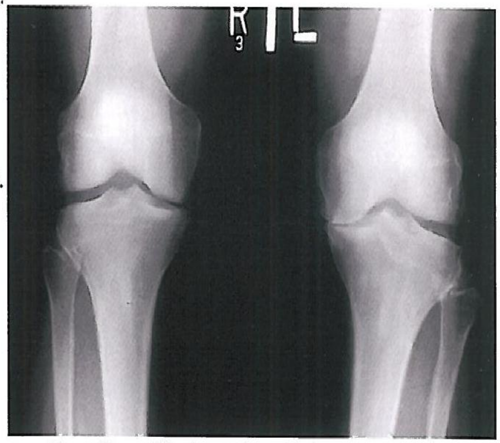
- It is ***associated with*** a **known cause** such as rheumatoid or another inflammatory arthritis, trauma, metabolic or endocrine disorders and congenital factors.

➢ Pathophysiology:-

- **Primary** and **secondary osteoarthritis** are ***not separable*** on a **pathologic basis.**
- ***Normal Cartilage***;
  - ***Structure***;
    - **Articular cartilage** is ***hyaline cartilage*** and is **2-4 mm *thick***.
    - **Articular cartilage *does not have* blood vessels, nerves** or **lymphatics.**
    - It is composed of a ***dense* extracellular matrix (ECM)** with a sparse distribution of ***highly specialized cells*** called **chondrocytes** (2-5%).



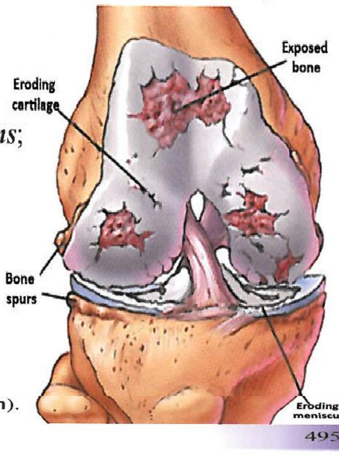
    - **Nutrition** is ***supplied to*** the **chondrocytes** by **diffusion**.
    - The **ECM** is ***principally composed*** of **water** (75-85%), **collagen**, and **proteoglycans**, with ***other* non-collagenous proteins** and **glycoproteins** present in ***lesser amounts***.
    - **Chondrocytes** are ***responsible for*** the **development**, **maintenance** and **repair** of **ECM.**
  - ***Function***;
    - Its ***principal function*** is to ***provide*** a **smooth, lubricated *surface for* articulation** and to ***facilitate*** the ***transmission*** of **loads** *with* a ***low* frictional coefficient**.
    - **Cartilage** is ***easily* compressed**, losing up to 40% of its original height when a load is applied (Compression increases the area of contact and disperses force more evenly to underlying bone, tendons, ligaments, and muscles).
- ***Osteoarthritic Cartilage***;



X-ray films of the knee show joint space narrowing

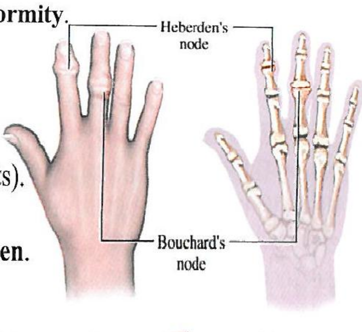
  - **Local mechanical *influences*, genetic factors, inflammation,** and ***aberrant* chondrocyte *function*** *leading to* ***loss of* articular cartilage.**
  - **OA *most commonly begins*** with **damage** to **articular cartilage**, *through* trauma or other injury, excess joint loading from obesity or other reasons, or instability or injury of the joint that causes abnormal loading.
  - The **chondrocyte *balance*** *between* **breakdown** and **resynthesis** of **cartilage** can be ***lost***, and a **vicious cycle** of ***increasing*** **breakdown** can *lead to* ***further* cartilage** loss.
  - **Inflammation** of the **synovium *can*** also **occur** (***often* mild** compared in rheumatoid arthritis).
  - **In *early* osteoarthritis, swelling** of the **cartilage** *usually occurs*.
  - ***Substantial loss*** of **cartilage** causes **joint space *narrowing*** and *leads to* a **painful, deformed joint.**
  - **Subchondral bone *lesions*** *may occur*.

➢ Signs, Symptoms and Clinical Manifestations:-

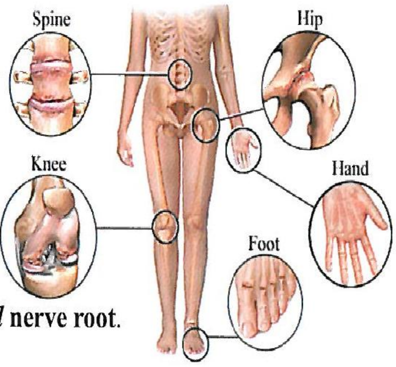


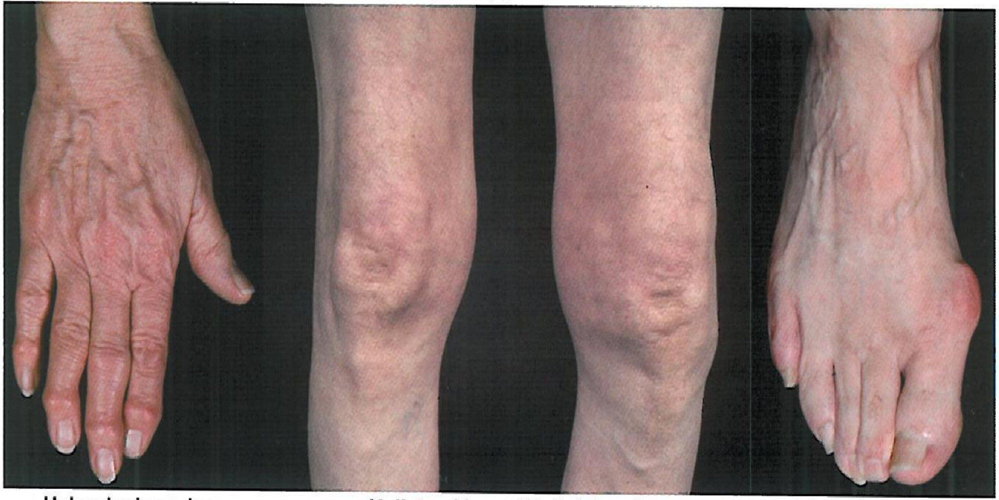
- **Pain**, **stiffness** & **locomotor restriction** are the ***main symptoms***;
- ***Joint Pain***;
  - Deep and **aching**.
  - ***Usually affects*** **1** to **few joints** at a *time*.
  - ***Slow progression*** *over* **months** to **years**.
  - ***May be*** **intermittent** and **relapsing**.
  - **Pain *with*** **motion** in ***early stage*** of disease.
  - **Pain *with*** **rest** in ***late stage*** of disease (**night pain**).
  - ***Often related*** to **weather** (**cold** can ***exacerbate*** **OA pain**).

- ***Stiffness***;
    - *Short-lived* (<30 min) ***early morning*** **stiffness.**
    - *Short-lived* (<30 min) ***inactivity-related*** **stiffness (gelling phenomenon**; *resolves with motion, recurs with rest*, i.e. like a gelatin, which remains liquid if kept moving and warm but solidifies if it sits).
- ***Swelling***; ***some patients*** *present with* **swelling** and/or **deformity**.
- ***Age***; *usually* **elderly** (>45 y).
- ***Hands***; **Hard bony enlargements**, ***called***;
    - **Heberden's nodes** (*distal* interphalangeal joints).
      and/or
    - **Bouchard's nodes** (*proximal* interphalangeal joints).
- ***Knee***;
    - ***Unilateral*** **knee OA** is ***more common*** in **young men.**
    - **Pain on patellofemoral** (*knee cap*) ***compression***.
    - **Pain** ***related to*** **climbing stairs.**



- ***Hips***;
    - **Groin pain** ***during*** **weight-bearing activities.**
    - **Stiffness**, *especially* ***after*** **inactivity.**
    - ***Limited*** **joint motion.**
- ***Spine***;
    - **L3 & L4** ***involvement*** is ***most common***.
    - ***Symptoms*** of **nerve root** ***compression***.
    - ***Loss*** of **reflexes.**
    - **Muscle weakness** ***associated with*** the ***affected*** **nerve root.**
- ***Feet***;
    - **First metatarsophalangeal (MTP) joint** ***involvement*** is ***most common***.

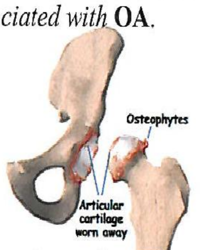




Heberden's nodes **Unilateral knee OA (left knee)** **First MTP joint OA**

➢ Diagnosis:-

- The ***diagnosis*** of **OA** is ***made through***; **history, physical examination, characteristic radiographic findings** and ***no specific*** **laboratory abnormalities** are *associated with* **OA.**
- ***Diagnostic Tests***;
    - **Joint Aspiration** (analysis of ***synovial fluid***);
        - In **OA** ***synovial fluid are***;
            - **Clear,** ***highly*** **viscous,** ***no*** **blood,** ***no*** **crystals,** ***no*** **infections.**
            - **Mild leukocytosis** {(<2,000 per mm^3 (2.0 × 10^9/L)}.
    - **Radiologic Evaluation**; can usually ***confirm*** the **diagnosis** of **OA.**
        - ***Loss*** of **joint space** and the ***presence*** of **new bone formation** or **osteophytes** (bone spurs).
    - **Laboratory Values**; *No specific test*, and **ESR** is ***normal*** in **OA.**
- *There is a specific criteria or scales for OA.*



➢ Rheumatoid Arthritis VS Osteoarthritis:-

	Rheumatoid Arthritis (RA)	Osteoarthritis (OA)
Cause	- ***Autoimmune*** damage of joints.	- ***Mechanical*** damage of joints.
Prevalence	- ***Less common*** than OA.	- ***Most common*** form of arthritis.
Age	- It may begin **any time** in life.	- It usually begins in **elderly** (> 45 y).
Onset	- ***Relatively*** **rapid**, ***over*** **weeks** to **months**.	- ***Slow***, ***over*** **years**.
Symptoms	- ***Symmetrically***. - **Pain, swelling, stiffness, redness** & **warmth**. - **Fatigue** & **low grade fever** in ***early stages***.	- ***Often begin*** on **one side** of the body. - **Pain** and **stiffness**. - ***No*** **whole-body symptoms**.
Joints	- ***Any joint*** can be **affected**. - *Can also* affects **other organs**.	- ***Weight-bearing joints***; **finger joints, hips, knees, spine** or **feet**.
Morning stiffness	- ***Long***-**lived** (**>30 min**).	- ***Short***-**lived** (**<30 min**) and ***returns*** at the **end of the day**.
Lab Values	- **Rheumatoid factor** (**RF**). - **Anti-Citrullinated Protein Antibodies** (**ACPA**). - **Erythrocyte Sedimentation Rate** (**ESR**). - **C-Reactive Protein** (**CRP**).	- ***No*** **specific test**.
Radiologic Evaluation	- *Search for*, **deformities**.	- *Search for*, **joint space narrowing** and/or **osteophytes**.

➢ Managements:-

- ***Treatment*** of **OA** *may* ***relieve*** **pain** or ***improve*** **function** but ***does not*** reverse *pre-existing* **damage** to the **articular cartilage**.
- ***Goals of treatments***;
  1) ***Educate*** the **patient, family members** and **caregivers**.
  2) ***Relieve*** **pain** and **stiffness**.
  3) ***Maintain*** or ***improve*** **joint mobility**.
  4) ***Limit*** **functional** ***impairment***.
  5) ***Maintain*** or ***improve*** **quality of life**.
- **Options**; **Treatment** ***depends*** on the **distribution** and **severity** of ***joint involvement***.
  - ***Optimally***, **patients** ***should*** **receive** a ***combination*** of **non-pharmacologic** and **pharmacologic therapies**.

Non-pharmacological Therapy

- **Education**; **patient education** ***about*** the **disease process**, the **extent of OA**, the **prognosis**, and **treatment options**, the **Arthritis Foundation** also *sponsors support* **groups** and **public education programs**.

- **Weight Loss**; there is a **link** ***between*** **obesity** and **osteoarthritis**, **weight loss** can ***decrease*** the **load** on a **weight-bearing joint** and ***decreased*** **symptoms** and **disability**.
- **Physical Therapy**; Physical therapy with **heat** or **cold treatments** and an ***exercise*** **program** ***helps to maintain*** **joint motion** and to ***reduce*** **pain** and **muscle spasms**.
- **Occupational Therapy**; **occupational therapists** also ***teach*** **patient** ***how*** to **protect** their **joints**, *such as* using both hands or using an assistive device.
- **Electromagnetic field stimulation and TENS**; BioniCare® is a ***pulsed*** **electromagnetic field stimulation device** has been ***used in*** patients with **knee osteoarthritis. Transcutaneous electrical nerve stimulation** (**TENS**) may be *another treatment option* for **pain relief**.
- **Acupuncture**; can be *used for* **pain** and **physical dysfunction** *associated with* **osteoarthritis**.
- **Assistive Devices & Orthoses**; ***Many patients*** with **osteoarthritis** ***more comfortable*** *wearing* **shoes** with *good shock-absorbing properties* or **orthoses**.

Pharmacological Therapy

- **Pharmacological therapy** in **OA** is *targeted at* **relief of pain**.
- For ***mild*** or ***moderate pain***, **topical analgesics** or **Paracetamol** *can be used*, ***if*** these **measures *fail***, or ***if*** there is **inflammation**, **NSAIDs** *may be useful*.
- ***Low-dose*** **opioid analgesics** *can be useful* for **patients** who experience ***no*** **pain relief** with **Paracetamol, NSAIDs, intra-articular glucocorticoid injections** or **topical therapy**.

Guidelines

➢ 2012 American College of Rheumatology (ACR) :-

For Hand Osteoarthritis

- ***Topical*** **Capsaicin**.
- ***Topical*** **non-steroidal anti-inflammatory drugs (NSAIDs)**, ***including*** **Trolamine Salicylate**.
- ***Oral*** **NSAIDs**, ***including*** **COX-2 selective inhibitors**.
- **Tramadol**.

** The ACR conditionally **recommends *against*** using **intra-articular *therapies*** or **opioid analgesics**.

** For ***patients*** **75 years & older**, the **ACR** conditionally ***recommends*** use **topical** *rather than* **oral NSAIDs**.

For Knee Osteoarthritis

- **Acetaminophen** (**Paracetamol**) (***up to*** **4 gm/day**).
- ***Oral*** **NSAIDs**.
- ***Topical*** **NSAIDs**.
- **Tramadol**.
- ***Intra-articular*** **corticosteroid injections**.

** The ACR conditionally recommend that patients with knee OA ***should not use*** the following; **Chondroitin sulfate**, **Glucosamine** or ***topical*** **Capsaicin**.

** The ACR has ***no recommendations*** regarding the use of ***intra-articular*** **Hyaluronates**, **Duloxetine** and **opioid analgesics**.

For Hip Osteoarthritis

- **Acetaminophen** (***up to*** **4 gm/day**).
- ***Oral*** **NSAIDs**.
- **Tramadol**.
- ***Intra-articular*** **corticosteroid injections**.

** The ACR conditionally recommend that patients with knee OA ***should not use*** the following; **Chondroitin sulfate** or **Glucosamine**.

** The ACR has ***no recommendations*** regarding the use of; ***topical*** **NSAIDs, *intra-articular*** **Hyaluronates**, **Duloxetine** and **opioid analgesics**.

➢ 2013 American Academy of Orthopedic Surgeons (AAOS):-

For Knee Osteoarthritis

- ***Oral*** **NSAIDs**.
- ***Topical*** **NSAIDs**.
- **Tramadol**.

** The AAOS was ***unable*** to **recommend *for* or *against*** the **use** of the following for symptomatic knee osteoarthritis: **Acetaminophen**, **Opioids**, **Pain patches**, **Intra-articular corticosteroid injections**, **Growth factor injections** and/or **platelet rich plasma (PRP)**.

** The AAOS ***does not*** **recommend** treatment with any of the following:

- **Intra-articular Hyaluronic acid**.
- **Glucosamine** and/or **Chondroitin sulfate** or **hydrochloride**.

- ***In 2016***; a large-scale analysis; researchers found that **Paracetamol** *does not* meet the minimum standard of clinical effectiveness in reducing pain or improving physical function in patients with knee and hip osteoarthritis.

Other Therapies

Glucosamine and Chondroitin

Glucosamine *and* Chondroitin

- **Glucosamine** ($C_6H_{13}NO_5$) [gloo-KOE-sa-meen] is an ***amino sugar*** (*amino-saccharide*).
- **Glucosamine**, acting as a ***substrate*** for the **biosynthesis** of **glycosaminoglycan *chains***, **aggrecan** and *other* **proteoglycans** of **cartilage**.
- *In vitro*, **Glucosamine** has been demonstrated to ***reduce*** **Prostaglandin E2**.

- **Chondroitin** [kon-DROY-tin] is a **Glycosaminoglycan** (**GAG**) *composed of* a chain of ***alternating sugars*** (**N-acetylgalactosamine** and **Glucuronic acid**).
- **Chondroitin** is an ***important structural*** **component** of **cartilage**.

- The ***exact role*** of **Glucosamine**, **Chondroitin**, or a ***combination*** of the two products is ***still unclear***.
- ***Dosing*** *should be* at ***least*** **1,500 mg/day** of **Glucosamine** and **1,200 mg/day** of **Chondroitin**.
- **Glucosamine** and **Chondroitin** are marketed in the **US** as ***dietary supplements*** and ***not approved*** by the **FDA**.
- **Glucosamine** *may*; **1**) Increase risk of bleeding. **2**) Increase blood pressure. **3**) Affect insulin resistance and/or blood sugar levels. **4**) Increased cataract risk or dry eyes. **5**) Use cautiously in people who have asthma, kidney disorders, active peptic ulcer disease and depression.

Hyaluronates Injection

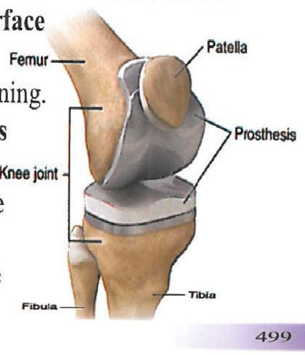
Hyaluronic Acid (HA) | Hyaluronate Sodium

- **Hyaluronic Acid** (**HA**) [HYE-a-loo-RON-ik AS-id] or **Hyaluronate Sodium** [HYE-a-loo-RON-ate SOE-dee-um] are available for ***intra-articular injection*** for treatment of **knee OA**.
- ***Main functions***; as a ***tissue lubricant***.
- **HA injections** ***temporarily*** and ***modestly increase*** **viscosity**.
- ***Intra-articular*** **HAs** ***approved by*** the **FDA** for the treatment of **osteoarthritic knee pain**.
- **HA** ***preparations***: *these agents are* ***expensive***;
  - **Hyalgan®** (20 mg sodium hylaronate/2 mL); weekly for 5 injections.
  - **Supartz®** (25 mg sodium hylaronate/2.5 mL); weekly for 5 injections.
  - **Euflexxa®** (20 mg sodium hylaronate/2 mL); weekly for 3 injections.
  - **Synvisc®** (16 mg hylan polymers/ 2 mL); weekly for 3 injections.
  - **Synvisc®-One** (48 mg hylan polymers/6 mL); single dose with efficacy up to 26 weeks.
  - **Orthovisc®** (30 mg hyaluronan/2 mL); weekly for 3 injections.
- ***Other uses*** of **HA**;
  - In **Ophthalmic Viscosurgical Device** (**OVD**); is ***viscoelastic solution*** used in **eye surgery**.
  - **Skin care** and **lip augmentation**; ***creams***, ***serums***, ***injections*** (Restylane®) and as ***oral supplements***; **increases in skin moisture** and **decrease wrinkles**.

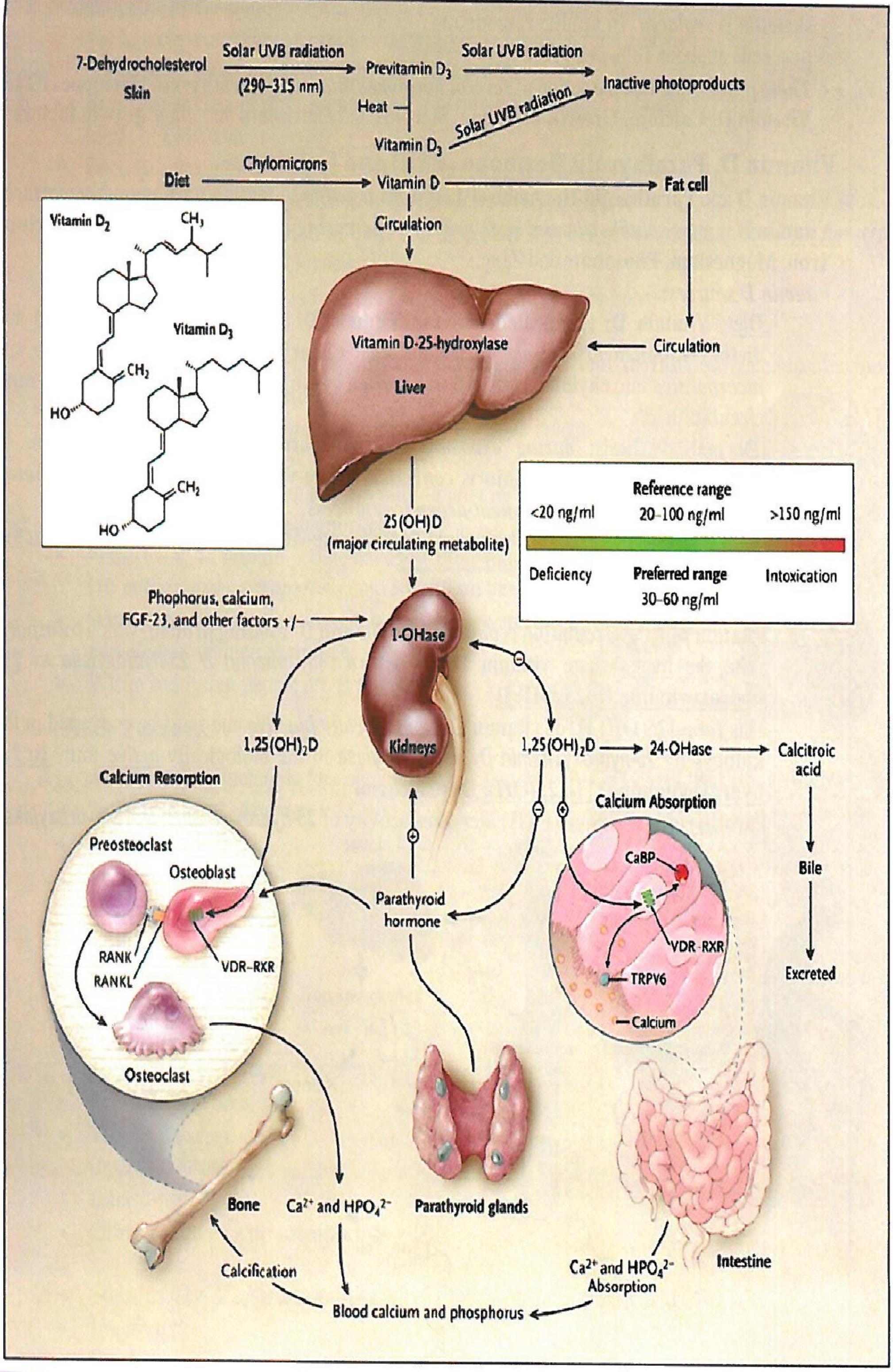
Surgery Therapies

- **Patients** whose **symptoms** are ***not adequately controlled*** with **medical therapy** and who have ***moderate*** to ***severe*** **pain** and ***functional impairment*** are *candidates for* **orthopedic surgery**.
- ***Orthopedic Surgery in OA***;
  - ***Arthroscopy*** (*Key-hole surgery*); used to ***smooth*** a **rough joint surface** by ***remove*** **loose cartilage** or **bone fragments**.
  - ***Joint Lavage*** (*Joint wash out*); used to therapeutic washing & cleaning.
  - ***Osteotomy*** (*Correction of deformity*); used to ***correct*** **certain defects** in the **hip** and **knee**, by **cutting** *through a* **bone**.
  - ***Arthroplasty*** (*Joint replacement*); used to **removal** of **joint surface** and the ***insertion*** of a **metal** and **plastic *prosthesis***.
  - ***Arthrodesis*** (*Fusion of joint*); used to ***union*** of **bones** on either side of the joint, by using **fusion bolts** and **beams**.

Total knee replacement

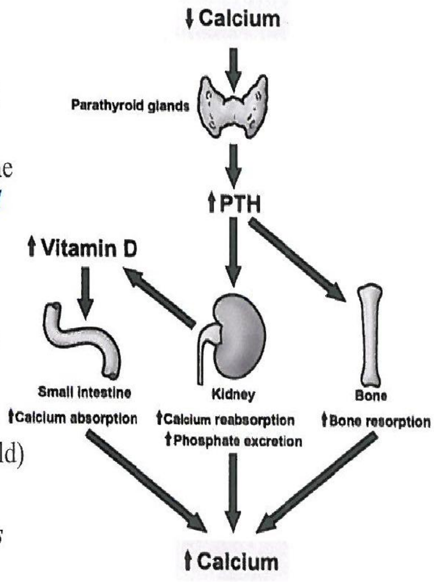


  - **Calcitriol** *binds* to the ***intestinal*** **vitamin D receptor** and then ***increases*** **calcium binding protein**. As a result, ***increase*** **intestinal absorption** of **Calcium** and **Phosphorous**.
    - Calcium absorption under normal conditions is approximately 30% to 40%, decreasing to 10% to 15% with low vitamin D concentrations.
  - **Vitamin D receptors** are also ***found*** in **many tissues**, such as **bone, intestine, brain, breast, colon, heart, stomach, pancreas, lymphocytes, skin** and **gonads**.
- ***Vitamin D, Parathyroid Hormone (PTH) and Calcium Regulation***;
  - ***Serum*** **calcium** *level* and *other factors* regulates production of **$1\alpha,25(OH)_2$ D** and **PTH**.
- ***Calcitonin Hormone*** ***inhibits*** osteoclastic *bone resorption*, ***decreases*** serum calcium, ***opposing*** the *effects* of PTH.


7-Dehydrocholesterol
Skin
Solar UVB radiation
(290–315 nm)
Previtamin D3
Solar UVB radiation
Inactive photoproducts
Heat
Solar UVB radiation
Vitamin D3
Diet
Chylomicrons
Vitamin D
Fat cell
Circulation
Vitamin D2
CH3
Vitamin D3
CH2
HO
Vitamin D-25-hydroxylase
Liver
Circulation
25(OH)D
(major circulating metabolite)
Reference range
<20 ng/ml
20–100 ng/ml
>150 ng/ml
Deficiency
Preferred range
30–60 ng/ml
Intoxication
Phophorus, calcium,
FGF-23, and other factors +/−
1-OHase
Kidneys
1,25(OH)2D
1,25(OH)2D
24-OHase
Calcitroic acid
Bile
Excreted
Calcium Resorption
Preosteoclast
Osteoblast
RANK
RANKL
VDR-RXR
Osteoclast
Parathyroid hormone
Calcium Absorption
CaBP
VDR-RXR
TRPV6
Calcium
Bone
Ca2+ and HPO42−
Parathyroid glands
Calcification
Blood calcium and phosphorus
Ca2+ and HPO42−
Absorption
Intestine

➢ Parathyroid Hormone (PTH) Functions:-

- *Bone*; *enhance* release of Calcium from the large bones (bone resorption) by *osteoclasts*.
- *Kidney*; *enhance* reabsorption of Calcium and *inhibit* reabsorption of Phosphate.
- *Intestine*; *enhance* absorption of Calcium in the *intestine* by *increasing* production of *activated* vitamin D (Calcitriol).


↓ Calcium
Parathyroid glands
↑ PTH
↑ Vitamin D
Small intestine
↑ Calcium absorption
Kidney
↑ Calcium reabsorption
↑ Phosphate excretion
Bone
↑ Bone resorption
↑ Calcium

➢ Bone Mineral Density (BMD):-

- **Bone density** or **bone mineral density** (BMD); is the *amount* of bone mineral in bone tissue.
- Women and men *begin* to *lose* a small amount of bone mass *starting in* the third (20-29 years old) to fourth (30-39 years old) decade of life.
- Bone density *measurement* is used in *diagnosis* of osteoporosis and fracture risk.

➢ Classifications and Etiology:-

- *Osteoporosis* is initially *divided into* **primary** and **secondary** osteoporosis.

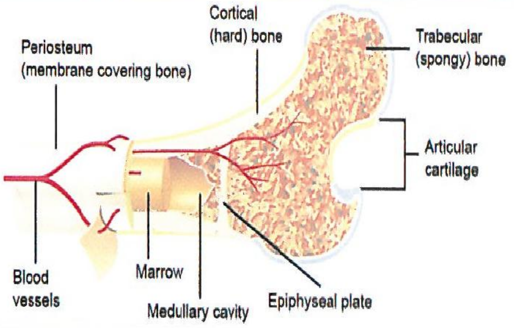
Primary Osteoporosis

Idiopathic Juvenile Osteoporosis (IJO)

- *Usually occurs* in children or young adults of *both* sexes.
- *Age of onset*: usually 8-14 years.
- *Rare* form of osteoporosis.
- *Normal* gonadal function.

Postmenopausal Osteoporosis (Type I Osteoporosis)

- *Mainly* as a result of the *loss* in ovarian hormone *production*, *specifically* Estrogen.
- Estrogen *deficiency increases proliferation*, *differentiation*, and *activation* of new osteoclasts and *prolongs* survival of mature osteoclasts.
- *Characterized by* a phase of *accelerated* bone loss, *primarily* from trabecular bone, leading to vertebral and wrist *fractures*.


Cortical
(hard) bone
Periosteum
(membrane covering bone)
Trabecular
(spongy) bone
Articular
cartilage
Blood
vessels
Marrow
Medullary cavity
Epiphyseal plate

Age-associated or Senile Osteoporosis (Type II Osteoporosis)

- *Occurs in* women and men as BMD *gradually* declines *with* aging.
- Bone loss *associated with* aging.
- Fractures *occur in* cortical and trabecular bone.
- Wrist, vertebral and hip fractures often also occur.

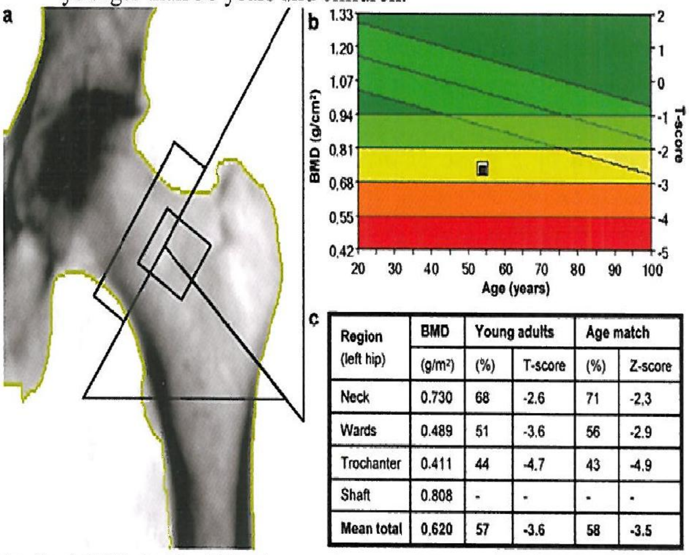
Secondary Osteoporosis

- Secondary osteoporosis *occurs* when an **underlying disease, deficiency** or **drug** *causes* osteoporosis.
- *Causes of Secondary Osteoporosis*;
  1) **Genetic**; *such as* renal hypercalciuria (*elevated calcium in the urine*).
  2) **Endocrine disorders**; *such as* hypogonadism, estrogen deficiency, hyperthyroidism, hyperparathyroidism, acromegaly, Cushing syndrome and diabetes mellitus.
  3) **Deficiency states**; *such as* calcium and vitamin D deficiency, malabsorption and malnutrition.
  4) **Inflammatory diseases**; *such as* inflammatory bowel disease and rheumatoid arthritis.
  5) **Neoplastic diseases**; *such as* multiple myeloma, leukemia, sickle cell anemia and thalassemia.
  6) **Medications**; *such as* glucocorticoids, anticonvulsants, thyroid replacement drugs, aromatase inhibitors, selective serotonin reuptake inhibitors (SSRIs), heparin (long term), medroxyprogesterone (Depo-Provera®), AIDS/HIV medications, furosemide, gonadotropin-releasing hormone (GnRH) analogs, thiazolidinediones (pioglitazone, rosiglitazone) & proton pump inhibitors (long-term).

➢ Diagnosis:-

- ***Physical Examination***;
  - **Risk factors assessment** (age, race, sex, previous fracture, body mass index, glucocorticoid use, current smoking, alcohol use, rheumatoid arthritis or other secondary causes).
  - **Personal history of fracture.**
  - **Bone pain** or **postural changes.**
  - **Loss of height** (greater than 3.8 cm).
  - **Low body weight** (body mass index < 19 kg/m²).

- ***Bone Mineral Density (BMD) Measurement***;
  - **Dual-Energy X-ray Absorptiometry (DXA or DEXA) device**; is the **gold standard** for **osteoporosis** ***diagnosis***;
    - ***Mechanism***;
      - Two X-ray beams, with different energy levels, are aimed at the patient's bones.
      - When soft tissue absorption is subtracted out, the BMD can be determined from the absorption of each beam by bone.
    - ***Types***;
      - **Peripheral DXA**; measures bone density in the finger, hand, forearm or foot (*low amount of radiation*).
      - **Central DXA**; measures bone density in the hip and spine.
    - ***Results***;
      - **T-score**; It is the value compared to the young adult (30-40 year old) of same gender.
        - ***Normal***; -1.0 or higher.
        - ***Osteopenia***; between -1.0 and -2.5.
        - ***Osteoporosis***; -2.5 or lower.
      - **Z-score**; It is the value compared with that of persons matched for age and sex.
        - ***Abnormal bone loss***; -2.5 or lower.
        - ***It is used in the following patients***: premenopausal women, men younger than 50 years and children.



Region (left hip)	BMD	Young adults		Age match	
	(g/m²)	(%)	T-score	(%)	Z-score
Neck	0.730	68	-2.6	71	-2,3
Wards	0.489	51	-3.6	56	-2.9
Trochanter	0.411	44	-4.7	43	-4.9
Shaft	0.808	-	-	-	-
Mean total	0,620	57	-3.6	58	-3.5

Results of DEXA showing BMD, T-score, Z-score and % compared to indicated reference population (young adults, age match) at different regions of the left hip and mean values

- ***Calculation Tools***;
  - **Fracture Risk Assessment Tool (FRAX®)**;
    - It was developed by the World Health Organization (WHO) task force in 2008 to provide a prediction tool for assessing an individual's risk of fracture.
    - It uses risk factors in addition to DXA measurements for improved fracture risk estimation.
    - The risk is expressed as a percentage: for example, 10% means 10 people out of a 100, with this level of risk, will develop osteoporosis in the next 10 years.
    - For online calculation, visit; www.shef.ac.uk/FRAX/tool.jsp

- *Laboratory Tests*;
  - * **Serum 25(OH) Vitamin D**;
    - **Osteomalacia**, **rickets** or **severe vitamin D deficiency**; < 12 ng/mL (< 30 nmol/L).
    - **Insufficient value for bone**; 12 to < 20 ng/mL (30 to < 50 nmol/L).
    - **Optimal value for bone health**; ≥ 20 ng/mL (≥ 50 nmol/L).
    - **Emerging evidence links potential adverse effects**; > 50 ng/mL (≥ 125 nmol/L).
      - R; Institute of Medicine, Food and Nutrition Board. Dietary Reference Intakes for Calcium and Vitamin D. Washington, DC: National Academy Press, 2010.
  - **Serum Total Alkaline Phosphatase**;
    - *Usually* ***normal*** in **primary osteoporosis**, ***but*** may be ***elevated*** for **several months** ***after*** a **fracture**.
    - It is useful to detect conditions such as **Paget's disease**, **metastatic bone disease** & **osteomalacia**.
  - **Serum Total Calcium and Phosphate**;
    - *Usually* ***normal*** in **primary osteoporosis**.
    - It is useful to detect conditions associated with **hypercalcemia** (*such as primary hyperparathyroidism*) or **hypocalcemia** that can ***contribute to*** **secondary osteoporosis**.
    - It ***decreased*** in **osteomalacia** and **rickets** (**soft bones**).
    - *N.B.*; **Osteomalacia** in ***children*** is *referred to as* **rickets**.
  - **Parathyroid Hormone (PTH)**;
    - *Usually* required if serum calcium is abnormal, to help investigate the cause of the calcium abnormality.
  - *Other Tests to Detect Secondary Causes*;
    - **Complete Blood Count (CBC)**; useful to diagnose **leukemia**, **sickle cell anemia**, **thalassemia** and **multiple myeloma**.
    - **Serum Protein Electrophoresis (SPEP** or **SPE)**; useful to diagnose **multiple myeloma** which causes major bone loss.
    - **Thyroid Function Tests**; **hyperparathyroidism** has been associated with osteoporosis.
    - **Serum Testosterone** (*in men*); **hypogonadism** has been associated with osteoporosis.
    - **Follicle-stimulating hormone (FSH)** (*in women*); **Menopause** (high FSH level) has been associated with osteoporosis.
    - **24 hr Urine Cortisol**, **Midnight Salivary Cortisol** or **Overnight Dexamethasone Suppression Test** (*tests for cortisol hypersecretion*); **Cushing's syndrome** has been associated with osteoporosis.
- *Measurement of Bone Turnover Markers* (*BTMs*); is a biochemical ***monitoring*** of **bone metabolism** (by measurement of enzymes and proteins released during bone formation and during bone resorption)
  - *A summary list*;

Bone Resorption Markers (*bone loss*)	Bone Formation Markers
- C-telopeptide of collagen cross-links (CTx).	- Carboxy-terminal propeptide of type I collagen (PICP)
- N-telopeptide of collagen cross-links (NTx).	- Amino-terminal propeptide of type I collagen (PINP).
- Pyridinoline (PYD).	- Bone-specific alkaline phosphatase (BSAP).
- Deoxypyridinoline (DPD).	- Osteocalcin (OC).
- Urinary hydroxyproline.	
- Tartrate-resistant acid phosphatase (TRAP-5b).	
- Bone sialoprotein (BSP).	

➢ Managements:-

- *Goals*;
  - ***Reduce*** **pain** and **deformity**.
  - ***Improve*** **functional capacity**.
  - ***Improve*** **quality of life**.
  - ***Reduce*** **future falls** and **fractures**.
- **Osteoporosis management** are ***incorporates of both*** **non-pharmacologic** and **pharmacologic therapies**.

Non-pharmacological Therapy

(Bone-Healthy Lifestyle)

- *Diet*;

* **Calcium and Vitamin D**; **Calcium** *and* **Vitamin D** *Recommended Daily Intakes;*

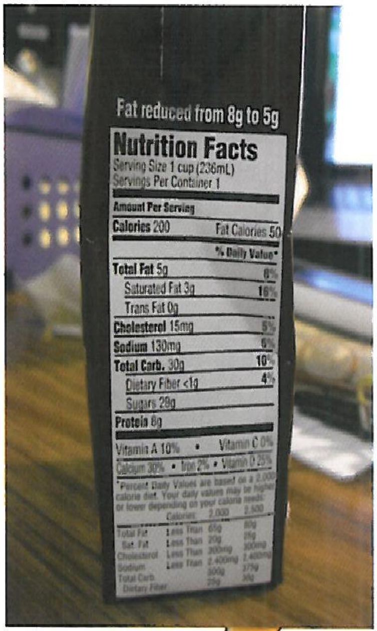
Ages	Elemental Calcium (mg)	Vitamin D (units)
Infants		
0–6 months	200	400 (10 mcg)
7–12 months	260	400 (10 mcg)
Children/Adolescents		
1–3 years	700	600 (15 mcg)
4–8 years	1,000	600 (15 mcg)
9–18 years	1,300	600 (15 mcg)
Adults		
19–50 years	1,000	600 (15 mcg)
51–70 years	1,000/male and 1,200/female	600 (15 mcg)
≥ 70 years	1,200	800 (20 mcg)

R; Insitute of Medicine, Food and Nutrition Board. Dietary Reference Intakes for Calcium and Vitamin D. Washington, DC: National Academy Press, 2010.

- A **one-cup** serving of ***most*** **dairy products** contains **200-300 mg** of **calcium.**
- There are only a ***few foods*** that naturally contain any **Vitamin D**; *such as* **cod liver oil** (has a great source; 1,360 IU in 1 tablespoon), salmon, tuna fish, milk and orange juice.

Nutrition Facts in Food or Supplements

- **Calcium**;
  - To calculate the amount of calcium in a serving of food, consumers can add a zero to the percentage of the daily value listed on food labels.
  - *For example*; a serving of milk has 30% of the daily value of calcium. This translates to 300 mg calcium per serving.
- **Vitamin D**;
  - To calculate the amount of vitamin D in a serving of food, multiply the % daily value of vitamin D listed on the food label by 4.
  - For example, a serving food (or milk) has 25% of the daily value of vitamin D. This translates to 25 X 4 = 100 units of vitamin D per serving.



Fat reduced from 8g to 5g

Nutrition Facts

Serving Size 1 cup (236mL)
Servings Per Container 1

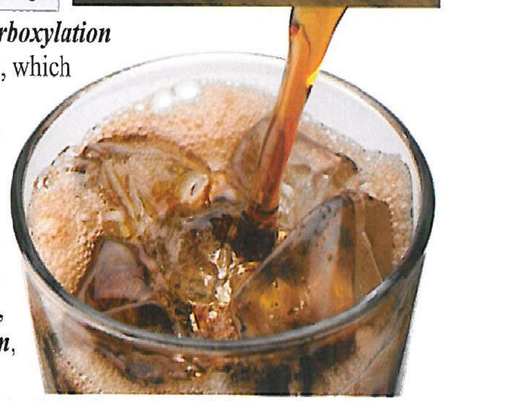
Amount Per Serving	
Calories 200	Fat Calories 50
	% Daily Value*
Total Fat 5g	8%
Saturated Fat 3g	16%
Trans Fat 0g	
Cholesterol 15mg	5%
Sodium 130mg	5%
Total Carb. 30g	10%
Dietary Fiber <1g	4%
Sugars 28g	
Protein 8g	

Vitamin A 10% • Vitamin C 0%
Calcium 30% • Iron 2% • Vitamin D 25%

*Percent Daily Values are based on a 2,000 calorie diet. Your daily values may be higher or lower depending on your calorie needs:

	Calories	2,000	2,500
Total Fat	Less Than	65g	80g
Sat. Fat	Less Than	20g	25g
Cholesterol	Less Than	300mg	300mg
Sodium	Less Than	2,400mg	2,400mg
Total Carb		300g	375g
Dietary Fiber		25g	30g

- **Vitamin K**; **Vitamin K** is a cofactor for ***carboxylation*** (*activation*) of proteins, such as **Osteocalcin**, which are involved in **bone formation.**
- **Dietary Soy**; **Soy Isoflavones** are naturally occurring ***selective*** **estrogen receptor modulators**, with ***potential*** **bone protective** ***effects***.



- *Alcohol*; *excessive* **Alcohol intake *increases* osteoporosis *risk*** *because* of **poor nutrition, *impaired* calcium** and **vitamin D *metabolism***, and an ***increased*** **risk for falls.**
- *Carbonated Beverages*; **Phosphorus** intake (*soft drinks such as Cola*): ***reduced*** **bone mineral density (BMD)** and ***increased*** **fracture risk.**
- *Caffeine*; *excessive* **Caffeine *consumption*** is *associated with* ***increased*** **calcium *excretion*** and ***increased*** **rates** of **bone loss.**

- ***Sodium***; *excessive* **Sodium** ***intake*** *is associated with* ***increased*** **calcium** ***excretion***.
- ***Smoking***; **Cigarette smoking** is a ***risk factor*** for **osteoporosis**, studies have shown a direct relationship between tobacco use and ***decreased*** **bone density**.
- ***Exercise***; **Exercise** can ***decrease*** the **risk of falls** and **fractures** by ***stabilizing*** **bone density** and ***improving*** **muscle strength**, **coordination**, **balance** and **mobility**.
- ***Fall Prevention***; **Patients** *should be* ***educated*** on **personal** and **home** ***safety options*** to ***decrease*** **falls**.

Pharmacological Therapy

- ***Currently***, **no** treatment can ***completely reverse*** *established* **osteoporosis**.
- **Non-pharmacologic therapy** *alone* are ***frequently*** **insufficient** to ***prevent*** or ***treat*** **osteoporosis**, **pharmacologic therapy** is ***often necessary***.
- ***Combination*** of *adequate* **Calcium** and **Vitamin D** ***intakes*** with **bisphosphonates** are the ***medication of choice***.

➢ Medications Used to Prevent and Treat Osteoporosis:-

Calcium & Vitamin D Supplementation

Calcium (Osteocare®)

- ***Commonly used*** **Calcium supplements** include **Calcium Carbonate** and **Calcium Citrate**.
- **Calcium Carbonate** is generally ***less*** **expensive** and has ***better absorption with*** **food**.
- ***Average daily*** **Calcium** ***dietary*** **intake** *needs* to be known to ***calculate*** **correct** ***safe*** **supplemental dose** (*see previous page; Calcium recommended daily intakes*).
- ***Most common side effects***; **Constipation**, **bloating**, **gas**, **stomach upset** and *rare* **kidney stones**.
- ***Common drug interactions***;
  - **Carbonate** ***decrease*** **absorption** with **Proton Pump Inhibitors** (**PPIs**).
  - **Calcium** ***decrease*** **absorption** of **Iron**, **Tetracycline**, **Quinolones**, **Bisphosphonates**, **Phenytoin** and **Levothyroxine**.
  - **Calcium** ***increase*** the **effects** of **Digoxin**.
  - **Calcium** ***induce*** **hypercalcemia** with **Thiazide Diuretics**.
  - **Calcium** ***decrease*** the **effects** of **Calcium Channel Blockers** (**Diltiazem** and **Verapamil**).

Vitamin D Preparations

- There are ***many types*** of **vitamin D preparations**, the ***two commonly*** available forms of vitamin D supplements are **Ergocalciferol** (**vitamin D_2**) and **Cholecalciferol** (**vitamin D_3**).
- **Vitamin D_2** and **Vitamin D_3** are ***not bioequivalent*** and ***should not*** be ***considered interchangeable***.
- **Vitamin D_3** is ***preferred over*** **Vitamin D_2**, because of its ***shorter half-life*** and ***decreased*** **potency** and **toxicity** (*little evidence*).
- ***Both*** **Vitamin D_2** and **Vitamin D_3** need to ***activation*** by ***hepatic metabolism*** to **25 (OH) vitamin D_3** and *then* ***renal metabolism*** to **$1\alpha,25(OH)_2$ vitamin D_3** (**Calcitriol**; *the active moiety*).
- ***Common side effects***; **Hypercalcemia**, (weakness, headache, somnolence, nausea, cardiac rhythm disturbance) and **hypercalciuria**.
- ***Common drug interactions***;
  - **Phenytoin**, **Barbiturates**, **Carbamazepine**, **Rifampin** ***increase*** **Vitamin D** ***metabolism***.
  - **Cholestyramine**, **Colestipol**, **Orlistat** and **Mineral oil** ***decrease*** **Vitamin D** ***absorption***.

Ergocalciferol (Drisdol®)

- **Ergocalciferol** [er-goe-kal-SIF-e-role] is an ***inactive form*** of **vitamin D** (**vitamin D_2**).
- ***Indications***; *treatment of* **hypoparathyroidism**, **vitamin D resistant rickets** and **familial hypophosphatemia**.
- ***Dose***;
  - **Vitamin D Resistant Rickets**: 12,000 to 500,000 IU units daily.
  - **Hypoparathyroidism**: 50,000 to 200,000 IU units daily.
  - **Dose for vitamin D deficiency**; 50,000 units (1.25 mg) once to twice weekly for 8–12 weeks; repeat as needed until therapeutic concentrations; occasionally 50,000 units monthly for maintenance.

Cholecalciferol (Devarol-S®) (Vi-De 3®) (Vidrop®)

- **Cholecalciferol** [KOE-le-kal-SIF-e-role] is an ***inactive form*** of **vitamin D (vitamin D_3)**.
- ***Indications***; **Vitamin D deficiency prevention and treatment.**
- ***Dose***; 400–1,000 units/day orally ***or*** 1,000–2,000 units IM every 3-6 months to achieve adequate intake.

Alfacalcidol or 1-hydroxycholecalciferol [1α (OH) D_3] (One-Alpha®)

- **Alfacalcidol** [al-fa-KAL-si-dol] is an ***inactive form*** of **vitamin D [1α (OH) D_3]**.
- ***Activation***; **Alfacalcidol** need only to ***activation*** by ***hepatic metabolism***.
- ***Indications***; ***Most commonly*** for **Vitamin D deficiency** in ***patients with*** **end stage renal disease** (due to impaired renal second hydroxylation step).
- ***Dose***; 0.25-1 µg/day orally ***or*** injection.

Calcitriol or 1,25-dihydroxycholecalciferol [1,25-$(OH)_2$ D_3] (Rocaltrol®)

- **Calcitriol** [KAL-si-TRYE-ol] is an ***active form*** of **vitamin D [1α, 25 $(OH)_2$ D_3]**.
- ***Activation***; **Calcitriol** ***not need activation***.
- ***Indications***; **hypocalcemia, renal osteodystrophy, hypoparathyroidism** and **secondary hyperparathyroidism.**
- ***Dose***; 0.25–0.5 mcg orally ***or*** 1–2 mcg/mL intravenously daily.

Dihydrotachysterol (Hytakerol®)

- **Dihydrotachysterol (DHT)** [dy-hy-dro-tak-is-TER-ol] is a ***synthetic vitamin D analog***.
- ***Activation***; ***activated*** in the **liver** that ***does not*** **require renal activation.**
- ***Indications***; **hypocalcemia, hypophosphatemia, rickets, osteomalacia, hypoparathyroidism, renal osteodystrophy** and **osteoporosis.**
- ***Dose***; ***in*** **osteoporosis**; 0.6 mg orally once a day.
- **19-nor-1,25-dihydroxyvitamin D2 (Paricalcitol)** and **Calcipotriene** or **Calcipotriol** are ***analogs of*** **Calcitriol** are ***approved for*** treatment of ***secondary hyperparathyroidism*** in *patients with* **chronic kidney disease. Calcipotriene** is ***approved for*** topical treatment of **psoriasis.**

Antiresorptive Medications

- Are agents that act by ***slowing*** **bone loss** by ***inhibiting*** the ***function*** of **osteoclasts.**

Bisphosphonates (BPs)

- **Bisphosphonates** are ***potent*** **bone resorption inhibitors** and ***most commonly*** *prescribed* **antiresorptive medications** and ***remain*** **first-line** ***treatment for*** **osteoporosis.**
- **Bisphosphonates** (P-C-P) are ***biological analogues*** of naturally occurring **pyrophosphates** (P-O-P)
- They are ***called*** **bisphosphonates** because they have ***two*** **phosphonate** ***groups.***

  Pyrophosphates are byproducts of ATP metabolism but have no biological activity because of the ubiquitous presence of pyrophosphatases
- **Bisphosphonates** are ***used*** to treat **osteoporosis, Paget's disease** and ***certain types*** of cancer (***such as*** **bone metastasis** and **multiple myeloma**).
- ***Oral*** and ***intravenous*** formulation of **Bisphosphonate** are ***available.***

Alendronate (Fosamax®)	**Ibandronate** (Boniva®)	**Risedronate** (Actonel®)
Zoledronic acid (Zometa®)	**Pamidronate** (Aredia®)	**Clodronate** (Loron®)
Etidronate (Didronel®)	**Neridronate** (Nerixia®)	**Tiludronate** (Skelid®)

- **Bisphosphonates** ***including***; **Alendronate** [a-LEND-row-nate], **Ibandronate** [eye-BAN-dro-nate], **Risedronate** [rih-SED-row-nate], **Zoledronic** [zole-DROE-nick] **acid** ***or*** **Zoledronate** [zole-dro-nate], **Pamidronate** [pah-MID-row-nate], **Clodronate** [KLO-dro-nate], **Etidronate** [e-TID-row-nate], **Neridronate** [NE-re-dro-nate] and **Tiludronate** [till-UH-droe-nate].
- **Alendronate, Neridronate, Ibandronate, Pamidronate, Risedronate** and **Zoledronic acid** have a ***nitrogen group*** and are *called* **nitrogen-containing BPs** (2nd and 3rd generation).
- ***Non*-nitrogen-containing BPs** are **Etidronate, Clodronate** & **Tiludronate** (1st generation).

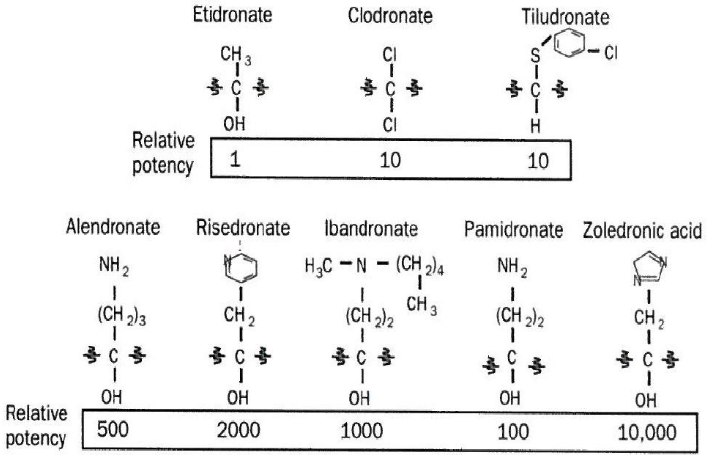
** **Alendronate, Ibandronate, Risedronate** and **Zoledronate** are the ***most popular first-line*** **bisphosphonate** used in **osteoporosis** and **Paget's.**

** **Oral BPs; Alendronate, Ibandronate, Risedronate, Clodronate, Etidronate** & **Tiludronate.**

** **IV BPs; Ibandronate, Zoledronic acid, Pamidronate, Neridronate** & **Tiludronate**

Pharmaco Kinetics

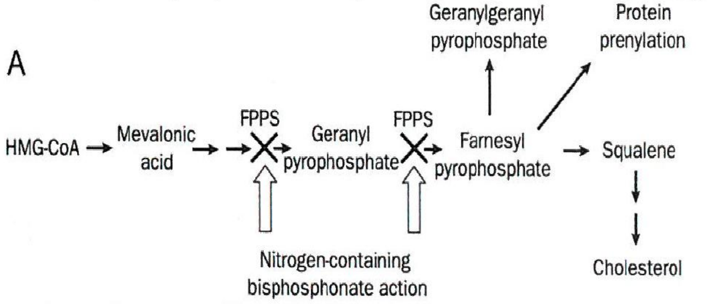
- **Oral bisphosphonates** are ***dosed on*** a **daily, weekly** or **monthly**.
- **IV bisphosphonates** are ***dosed on*** **quarterly** (3 months) or **yearly**.
- **Bisphosphonates** have an ***extremely high affinity*** for **bone tissue**.
- ***Absorption*** of **oral bisphosphonates** is ***very poor*** (<1-10%) by passive diffusion in the stomach and upper small intestine, **food** and ***other*** **medications** (*such as* **Calcium** & **Iron**) ***significantly decrease absorption***.
- 20-80% of ***absorbed*** **bisphosphonate** ***rapidly uptake*** by **bone** and the **remainder** ***rapidly excreted*** in the **urine**.
- **Bisphosphonates** ***once bound*** to **bone**, they are ***cleared over*** a *period of* **hours** to **years**.


Etidronate
Clodronate
Tiludronate
Relative potency
1
10
10
Alendronate
Risedronate
Ibandronate
Pamidronate
Zoledronic acid
Relative potency
500
2000
1000
100
10,000

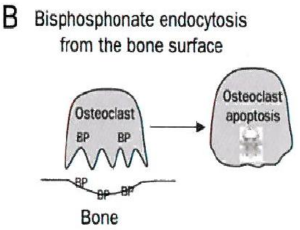
Mechanism OF Action

- **Bisphosphonates** ***decrease*** **osteoclastic bone resorption** ***through*** an ***increase*** in **osteoclastic apoptosis** (*programmed cell death*) and ***decrease*** **osteoclast activity**.
- ***In details***;

  A) **Nitrogen-containing bisphosphonates**;
    - Act by inhibiting farnesyl pyrophosphate (FPP) synthase (an enzyme in the mevalonate pathway; cholesterol biosynthetic pathway).
    - Inhibition of this enzyme in osteoclasts prevents the biosynthesis of isoprenoid lipids (FPP and GGPP) that are essential for osteoclast activity.


A
HMG-CoA
Mevalonic acid
FPPS
Geranyl pyrophosphate
FPPS
Farnesyl pyrophosphate
Geranylgeranyl pyrophosphate
Protein prenylation
Squalene
Cholesterol
Nitrogen-containing bisphosphonate action

  B) **Non–nitrogen-containing bisphosphonates**;
    - Act by incorporated into molecules of newly formed adenosine triphosphate (ATP) by the class II aminoacyl–transfer RNA synthetase.
    - Intracellular accumulation of these non-hydrolyzable ATP analogues is believed to be cytotoxic to osteoclasts because they inhibit multiple ATP-dependent cellular processes, leading to osteoclast apoptosis.


B
Bisphosphonate endocytosis from the bone surface
Osteoclast
BP
BP
BP
BP
BP
Bone
Osteoclast apoptosis

Side Effects

- **Oral bisphosphonates**;
  - **Stomach upset**, **inflammation** and **erosions** *of the* **esophagus** (main problem of oral N-containing preparations; see precautions and patient counselling).
  - **Musculoskeletal pain.**
- **IV bisphosphonates**;
  - **Fever** and **flu-like symptoms** (*acute inflammatory response*) after the *first* **infusion.**
  - **Osteonecrosis** *of the* **jaw (ONJ)** *especially with higher IV doses for the treatment of cancer.*
- *Uncommon Side Effects*;
  - ***Recent studies*** have reported **bisphosphonate** use (*specifically* **Zoledronate** and **Alendronate**) as a ***risk factor*** for **atrial fibrillation** in **women**.

*** Bisphosphonates Precautions ***

Patient Counselling

1) *Before starting bisphosphonates*; *evaluation for* **hypocalcemia**, **vitamin D deficiency** and **renal impairment** [*by measuring serum calcium, 25 (OH) D and serum creatinine*], hypocalcemia and/or vitamin D deficiency must be corrected.
2) *Each* **oral dose** *should be* taken *alone* on an *empty stomach* [*morning*] with *at least* **240 mL** of **tap water** (not coffee, juice, mineral water or milk) [enteric-coated delayed-release formulation (weekly) needs to be taken with only ~100mL] *at least* **30** (60 for **Ibandronate**) **minutes** *before* **consuming** *any* **food**, **supplements** (**Calcium**) or **medications** [*because bioavailability is very poor and to minimize GI side effects*].
3) **The patient** *should be remain* **upright** (*sitting or standing*) for *at least* **30 minutes** (60 for **Ibandronate**) [*to minimize esophagus ulceration*].
4) *If missed dose*;
   - *Weekly dose*; can take it the *next day*, if *more than* **1 day** the *dose is skipped until* the **next week.**
   - *Monthly dose*; it can be *taken* up to **7 days** *before* the **next administration.**
5) **Patient** *should* **take Calcium** and **Vitamin D** (**Calcium** ***should not take at the same time***; at least one hour after bisphosphonates); **Fosamax® Plus** & **Fosavance®**; **Alendronate** + **Cholecalciferol.**
6) *Should not* be **given** to *patients with* **active upper GI disease.**
7) *Should* be *discontinued* in *patients who* **develop** *any* **symptoms** of **esophagitis.**
8) *Delay* **bisphosphonate therapy** in **dental** *implant* or *extraction* for a *few* **months** *until* **healing** of the **jaw** is *complete*.
9) *Once-yearly administration of* **Zoledronic acid** *should be infused over at least* **15 minutes** with a **pump** [**Acetaminophen** or **ibuprofen** can be given to *decrease* **acute phase reactions**].

Dose

** For Osteoporosis **

- **Alendronate**; *For prevention*; 5 mg daily or 35 mg weekly - *For treatment*; 10 mg daily or 70 mg tablet (Fosavance®; 70 mg tablet + vitamin D 2,800 or 5,600 units), or 75 mL liquid weekly.
- **Risedronate**; 5 mg daily, 35 mg weekly, 75 mg for 2 days monthly, 150 mg monthly
- **Ibandronate**; 150 mg monthly, 3 mg intravenous quarterly (every 3 months).
- **Zoledronic acid**; - *For treatment*; 5 mg intravenous infusion yearly.
  - *For Prevention*; 5 mg intravenous infusion every 2 year.

Selective Estrogen Receptor Modulators (SERMs)

- **Selective estrogen receptor modulators** (**SERMs**) are a **class of drugs** that *act on* the **estrogen receptor**, *produce* **estrogenic** and **anti-estrogenic effects** ***depending on*** the **specific tissue** (**mixed estrogen agonist/antagonist; EAA**).
- **SERMs** are considered to provide the ***beneficial effects*** of **Estrogen** ***without*** the **potentially adverse *outcomes***.
- **SERMs** are ***used dependent*** on their **pattern of action in various tissues:**

SERMs	Generation	Uses	Estrogen Receptor; Location
Clomiphene	First	Ovulation Induction	***Antagonist***; hypothalamus.
Tamoxifen **Toremifene**	First	Breast Cancer	***Agonist***; bone and uterus. ***Antagonist***; breast.
Raloxifene	Second	Osteoporosis - Breast Cancer	***Agonist*** (***Full***); bone. ***Antagonist***; breast and uterus.
Ormeloxifene	Third	Contraception	***Agonist***; bone. ***Antagonist***; breast and uterus.
Lasofoxifene	Third	Osteoporosis - Breast Cancer - Vaginal Atrophy	***Agonist***; bone ***Antagonist***; breast and uterus.
Ospemifene	Third	Vaginal Atrophy - Dyspareunia	***Agonist***; bone ***Antagonist***; breast and uterus.
Bazedoxifene	Third	Osteoporosis	***Agonist*** (***Full***); bone. ***Antagonist***; breast and uterus.
Arzoxifene	Third	Osteoporosis (*clinical phases*)	***Agonist*** (***Full***); bone. ***Antagonist***; breast and uterus.

- **Femarelle** is a ***dietary supplement*** that may act as a **SERM**, it can ***reduce*** the **risk** for **osteoporosis**.

Raloxifene (Evista®)

- **Raloxifene** [rah-LOX-ih-feen] is a ***selective*** **estrogen receptor modulator** (**SERM**) ***approved for*** the ***prevention*** and ***treatment*** of **osteoporosis in postmenopausal women**.
- It has ***estrogen-like effects*** on **bone** and ***estrogen antagonist effects*** on **breast** and **endometrium**.
- It is ***FDA-approved*** for ***reduction*** in **risk** of **invasive breast cancer**.
- ***Supplemental*** **Calcium** and **Vitamin D** ***should be*** **added**.
- **Raloxifene** causes some ***positive*** **lipid effects**; ***reduces*** levels of **total cholesterol** and **low density lipoprotein** (**LDL**) **cholesterol**.
- ***Dose***; 60 mg orally once a day.
- ***Common side effects***; **hot flashes** and **leg cramps**.
- ***FDA black box warning***; ***risk*** of ***venous thromboembolism*** and **death** *due to* **stroke**.
- ***Pregnancy***; **Raloxifene** is a **teratogenic drug** (**Category X**).
- ***Contradictions***; **lactating women** or **pregnant women** and in **women** with ***active*** or ***past history*** of **venous thromboembolic events**.

Bazedoxifene (Viviant®)/Conjugated Estrogens (Premarin®) OR Bazedoxifene/Conjugated Estrogens (Duavee®)

- **Bazedoxifene** [ba-ze-dox-i-feen] is a ***third generation*** ***selective*** **estrogen receptor modulator** (**SERM**), *developed by Pfizer*.
- **In 2013, Duavee®** (**Bazedoxifene/Conjugated Estrogens**) *approval for* ***prevention*** (*not treatment*) of **postmenopausal osteoporosis**.
- **Conjugated Estrogens**; are ***blended equine*** **estrogens**, which may include estrone sulfate, equilin sulfate and equilenin sulfate.
- **Conjugated Estrogens** are ***added*** to;
  - ***Reduced risk*** of **endometrial hyperplasia**.
  - ***Reduced*** **vasomotor symptoms** (**hot flashes**) of ***menopause***.
- ***Dose***; **Conjugated Estrogens** 0.45 mg and **Bazedoxifene** 20 mg orally ***once*** a day.
- ***FDA black box warning***; ***risk*** of; ***venous thromboembolism***, **endometrial/breast cancer** and **probable dementia**.
- ***Pregnancy***; **Category X**.

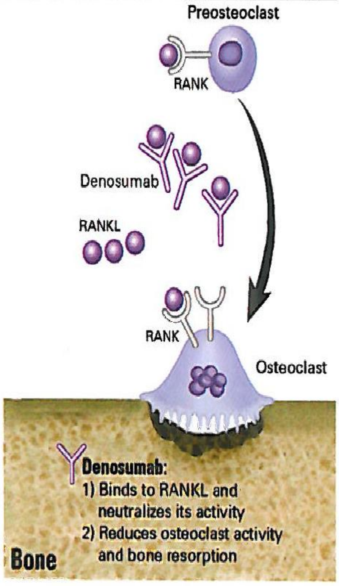
Calcitonin Hormone

Calcitonin (Miacalcic®) (Miacalcin®) (Fortical®)

- **Calcitonin** is an ***endogenous hormone released from*** the **thyroid gland** when ***serum*** **calcium** is ***elevated***, ***opposing*** the **effects** of **parathyroid hormone (PTH)**.
- It is ***produced*** either by **recombinant DNA technology** or by **chemical peptide synthesis** of **Salmon Calcitonin** (*Salmon fish*).
- **Calcitonin-Salmon** [KAL-si-TOE-nin SA-mon], is ***more potent*** and ***longer lasting*** than the **Mammalian Calcitonin**.
- *Mechanism of action*; **Calcitonin** ***lowers*** serum **calcium** levels in *two ways*:
  - *Major effect*: ***Inhibits*** **osteoclast activity** in bones.
  - *Minor effect*: ***Inhibits*** **renal reabsorption** of **calcium** & **phosphate** → *increase* **excretion**.
- *Indications*;
  - **Postmenopausal Osteoporosis** (> 5 years of postmenopause); **intranasal** ***preferred than*** **parenteral**.
  - *Acute management* **hypercalcemia** (*only IM or SC*).
  - *Symptomatic* **Paget's disease** (*only IM or SC*).
- *Because* **efficacy** is ***less than*** the ***other*** **antiresorptive therapies** (*such as* **bisphosphonates**), **Calcitonin** is *reserved as* ***third-line treatment***.
- *Dose*; In **Postmenopausal Osteoporosis**; - ***SC/IM***; 100 IU every other day.
  - ***Nasal Spray***: 1 spray (200 IU) daily.
- *N.B.*; In **osteoporosis** *ensure* **adequate Calcium** and **Vitamin D intake**.
- *Efficacy*; *Only* **vertebral fractures** *decrease* with ***intranasal*** **calcitonin therapy** (not affect hip).
- *Pregnancy*; Category C.
- *Warning*; - **Hypersensitivity reactions** (*anaphylaxis*).
  - **Malignancy.**
  - **Nasal adverse reactions** (*rhinitis*).
  - **Risk of hypocalcemia.**

Monoclonal Antibody

Denosumab (Prolia®) (Xgeva®)


Preosteoclast
RANK
Denosumab
RANKL
RANK
Osteoclast
Denosumab:
1) Binds to RANKL and neutralizes its activity
2) Reduces osteoclast activity and bone resorption
Bone

- **Denosumab** [den-OH-sue-mab] is ***a monoclonal antibody*** with *affinity* for **nuclear factor-kappa ligand (RANKL)**.
- *Mechanism of action*;
  - *Pre-osteoclast*; is an **osteoclast** *precursor*.
  - **RANK (receptor activator of nuclear factor-kappa B)** is a *surface* **receptors** in **osteoclast** and **pre-osteoclast**.
  - **RANK** is *activated by* **RANKL (RANK-Ligand)**.
  - **Activation** of **RANK** *by* **RANKL** *promotes* the *maturation* of **pre-osteoclasts** *into* **osteoclasts**.
  - **Denosumab** ***inhibits*** this **maturation** of **osteoclasts** by ***binding*** to and ***inhibiting*** **RANKL** → *decrease* **bone resorption**.
- *Indications*;
  - Prolia®; **Postmenopausal osteoporosis** (*with high risk of fracture*) *and* **bone loss** (*due to certain medications*).
  - Xgeva®; **Hypercalcemia** of **malignancy** and **bone metastases**.
- *Off-label*; **bone destruction** *caused by* **rheumatoid arthritis**.
- *Dose*; 60 mg SC as a single dose, once every 6 months.
- *N.B.*; *Ensure* adequate **Calcium** and **Vitamin D intake**.
- *Most common side effects*; **joint** and **muscle pain**, *increased* **risk of infections** (*cellulitis*) and **hypocalcemia, hypersensitivity allergy reactions, osteonecrosis** *of the* **jaw (ONJ)** and **atypical hip fractures**.
- *Pregnancy*; Category D.
- *Contraindications*; *Pre-existing* **hypercalcemia**.
- **Romosozumab** is an ***anti-sclerostin monoclonal antibody*** in development for the treatment of **osteoporosis in postmenopausal women** at *increased* **risk of fracture** (not approved yet; 10/2016).

Hormone Replacement Therapy (HRT)

- *Although* **Estrogens** are ***FDA indicated*** for ***prevention*** of **osteoporosis**, they should only be used ***short-term***, because adverse effects associated with estrogen therapy (e.g., risks for breast cancer, myocardial infarction, stroke, and venous thromboembolic events).
- **Hormone replacement therapy** (HRT) [**Estrogen** ***with*** or ***without*** **Progestogen**] is ***not currently*** **recommended** for the ***treatment*** of **osteoporosis.**

Anabolic Therapy

Parathyroid Hormone (PTH)

Teriparatide (Forteo®)

- **Teriparatide** [ter-ih-PAR-a-tide] is a ***recombinant form*** of **human parathyroid hormone** (**PTH**).
- It is the ***only*** available **anabolic agent** (*bone growing*) for the ***treatment of*** **osteoporosis.**
- *Mechanism of action*;
    - ***Endogenous*** **PTH** ***regulate*** **Calcium** and **Phosphate** *metabolism* in **bone** and **kidney**.
    - **PTH** ***increase*** **serum Calcium** by ***increasing*** **bone resorption** (chronically elevated **PTH** will deplete bone stores).
    - *However*, ***intermittent*** **exposure** to **PTH** (once-daily injections of **Teriparatide**) will ***activate*** **osteoblasts** ***more than*** **osteoclasts**, ***stimulating*** **new bone formation** *leading to* ***increased*** **bone mineral density**.
- **Teriparatide** ***increases*** **bone formation, bone remodeling rate, osteoblast number** ***and*** **activity**.
- **Teriparatide** is the ***first*** **drug** that ***stimulates*** **bone formation** (other agents inhibit bone resorption).
- *Indications*;
    - **Osteoporosis in men** (**primary** or **hypogonadal osteoporosis**); *with high risk for fracture.*
    - **Osteoporosis in postmenopausal women**: *with high risk for fracture.*
    - **Glucocorticoid-induced osteoporosis**; *with high risk for fracture.*
- *N.B.*; **Teriparatide** ***should be reserved for*** **patients** at ***high risk of fractures*** and those who have ***failed*** or ***cannot*** **tolerate** ***other*** **osteoporosis therapies.**
- *Off-label*; **Teriparatide** also ***accelerates*** **fracture healing.**
- *N.B.*; ***Ensure*** **adequate Calcium** and **Vitamin D intake** (before treatment, levels of serum **Calcium**, **PTH**, and **25(OH) D** need to be ***monitored***).
- *Dose*; SC injection 20 mcg once a day in the thigh or abdomen.
- *Pregnancy*; **Category C.**
- *Contraindications*;
    - **Teriparatide administration** ***not recommended more than*** **2 years** (safety and efficacy not been evaluated).
    - ***Pre-existing*** **hypercalcemia.**
    - ***Severe*** **renal impairment.**
    - **Metabolic bone diseases** ***other than*** **primary osteoporosis** (such as **hyperparathyroidism** and **Paget's disease**).
- *FDA black box warning*; **Teriparatide** has been ***associated with*** an ***increased risk*** of **osteosarcoma** (cancerous tumor in a bone) in **rats.**

Other Agents

Strontium Ranelate (Protelos®)

- **Strontium Ranelate** [stron-tee-um ran-ell-ate] is composed of **Ranelic acid** and **Strontium.**
- It ***increases*** **collagen** and **non-collagenic proteins** ***synthesis*** by ***mature*** **osteoblast enriched cells.**
- The effects on **bone formation** were ***confirmed*** by ***enhanced pre-*****osteoblastic cells replication.**
- **Strontium Ranelate** is ***not approved*** by the **US FDA**, ***but*** in the **United Kingdom** is ***prescribed.***
- ***Should be*** **taken 2 hours** ***before*** **food** or **other agents.**

➢ Guidelines Summary:-

- **American College of Physicians**;
  - All of the *following agents* ***should be*** accompanied by ***sufficient intake*** of **Calcium** and **Vitamin D**;
    - **Bisphosphonates**, **Raloxifene**, **Calcitonin**, **Denosumab** and **Teriparatide**.
- **American Association of Clinical Endocrinologists** (**AACE**) *2010*;
  - The following recommendations for choosing drugs to treat osteoporosis:
    - ***First-line agents***: **Alendronate**, **Risedronate**, **Zoledronic Acid**, **Denosumab**.
    - ***Second-line agent***: **Ibandronate**.
    - ***Second-*** or ***third-line agent***: **Raloxifene**.
    - ***Last-line agent***: **Calcitonin**.
    - **Patients** with ***very high*** **fracture risk** or in whom **bisphosphonate therapy** has ***failed***: **Teriparatide**.
- **National Osteoporosis Guideline Group** (**NOGG**) *2013 updates*;
  - **Recommendations** *include* the *following*;
    - * **Bisphosphonates**, **Denosumab**, **Teriparatide**, **Raloxifene** and **Strontium Ranelate**; **effective** to ***lower*** the **risk** for **vertebral fracture** (and **hip fracture** in *some cases*).
    - * **Alendronate** is usually ***first-line treatment***; because of its **1) broad spectrum** of ***anti-fracture*** **efficacy** and **2) low cost**.
    - * **Ibandronate**, **Risedronate**, **Zoledronic Acid**, **Denosumab**, **Raloxifene** or **Strontium Ranelate** may be ***appropriate therapy if*** **Alendronate** is ***contraindicated*** or ***poorly tolerated***.
    - * **Teriparatide** ***should be*** used ***only*** for patients at ***very high risk***, *especially for* **vertebral fractures**; ***because*** their **high cost**.
    - * **Postmenopausal women** may ***benefit from*** **Calcitriol** (*active* **Vitamin D**), **Etidronate**, and **hormone replacement therapy**.
    - * **Treatments for men** at ***increased*** **fracture risk** *include*; **Alendronate**, **Risedronate**, **Zoledronic Acid** and **Teriparatide**.
    - * **Patients** at ***increased*** **risk** *for* **fracture** or ***beginning*** **glucocorticoid therapy** ***should start*** **Alendronate** or ***other*** **bone-protective treatment**.
    - * ***For*** **postmenopausal women**, ***prevention*** and ***treatment*** of **glucocorticoid-induced osteoporosis** includes; **Alendronate**, **Etidronate**, and **Risedronate**; **treatment options** for ***both sexes*** are **Teriparatide** and **Zoledronic Acid**.
    - * **Calcium** and **vitamin D** ***supplementation*** is widely ***recommended for*** **older persons** and is ***often*** **recommended** as an **adjunct** to ***other*** **treatments** for **osteoporosis**.
    - * ***Withdrawal*** of **bisphosphonate** treatment is *associated with* ***decreases*** in **BMD** and **bone turnover** ***after*** **2-3 years** for **Alendronate** and **1-2 years** for **Ibandronate** and **Risedronate**.
    - * ***If*** **bisphosphonates** are ***discontinued***, **fracture risk** ***should be re-evaluated*** *after* ***every*** **new fracture**, or ***after*** **2 years** if ***no new*** **fracture occurs**.

- ***Finally***; **Bisphosphonates** are ***first-line therapy*** for **osteoporosis** in **postmenopausal women** *without* ***contraindications***. **Calcitonin** and **Raloxifene** are ***alternatives*** but may be less efficacious (especially for non-vertebral fractures). **Teriparatide** and **Denosumab** should be ***reserved for*** **patients** at ***high risk*** or those who ***fail other therapies***.